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The Effects of Heartworm Infection and Beta Blockade on Submaximal, Graded Exercise in Dogs.

Patricia Louise hopkins Price
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THE EFFECTS OF HEARTWORM INFECTION AND BETA BLOCKADE ON SUBMAXIMAL, GRADED EXERCISE IN DOGS

The Louisiana State University and Agricultural and Mechanical Col. PH.D. 1986

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THE EFFECTS OF HEARTWORM INFECTION AND BETA BLOCKADE ON SUBMAXIMAL, GRADED EXERCISE IN DOGS

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

in

The School of Health, Physical Education, Recreation
and Dance

by

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May, 1986

Dedicated

to

David

for his love,

patience, and understanding

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ABSTRACT

Four dogs with canine heartworm disease (CHD) and four control dogs were tested during a 21 minute submaximal, incremental, graded treadmill test, under normal conditions and after 2 mg/kg propranolol, i.v. Arterial and venous blood gas and pH, heart rate, systemic blood pressure, hematocrit, rectal temperature, lactate, glucose, and electrolytes were measured. CHD dogs had lower sodium and P_aO_2 levels. All dogs displayed progressive increments in heart rate, hematocrit, and potassium and small gains in rectal temperature during exercise. Mean arterial blood pressure (MABP) and arterial pH increased and remained elevated throughout exercise. P_vO_2 and P_aCO_2 decreased, but P_aO_2 did not change during exercise. At the onset of exercise, the responses of MABP, heart rate, hematocrit, potassium, arterial pH and P_aCO_2 at the onset of exercise were greater in the CHD dogs. There was a slight increment in lactate during exercise, but no difference in lactate between the two groups. Control dogs exhibited a slight increment in sodium and chloride levels in exercise, while CHD dogs did not.

At rest, propranolol increased glucose levels, which did not change during exercise. While propranolol increased P_aO_2 in CHD dogs, their values were still significantly lower than those of control dogs. P_aO_2 did not change during beta blocked exercise. MABP and heart rate were significantly lower at each stage of work following propranolol. During beta-blocked exercise, changes in lactate, sodium, chloride and hematocrit were similar to those in non-blocked exercise. Potassium

levels were greater in the beta-blocked exercise.

During both exercise tests, CHD dogs had consistently, but insignificantly, higher potassium, heart rate, and MABP values than control dogs. Dogs with CHD exhibited greater respiratory alkalosis at the onset of exercise. The CHD dogs' responses at the onset of exercise in heart rate and MABP indicated an exaggerated pressor response. The greater increments in hematocrit and potassium at the beginning of work suggested an enhanced alpha receptor response in the CHD dogs.

CHAPTER I

Introduction

The dog has been used in many areas of research, including studies of aging, arterial diseases, shock and blood pressure regulation, and the renal, respiratory and cardiovascular systems (Gay, 1984). The structure and function of dog respiratory and cardiovascular systems are similar to those of a small man (Gay, 1984), even though the shape of the thoracic cavity differs. With respect to exercise, there are some similarities and differences between the responses of the dog and those of man.

At the onset of exercise, both man and dog exhibited a two-phase response in ventilation (Dejours, 1966; Szlyk, McDonald, Pendergast & Krasney, 1981). Tidal volume and respiratory frequency increased abruptly in the initial fast phase, lasting about 4 s, and were independent of the intensity of the work. The second phase involved a more gradual increment until ventilation tended to plateau during steady state exercise. Raab, Eng, and Waschler (1976) felt dogs and humans had similar biochemical responses to running, because the metabolism of a dog running at various treadmill grades was like that of a human. Cerretelli, Piiper, Mangili and Ricci (1964a) studied anaerobic and aerobic metabolism in exercising dogs. They found that the dog's efficiency of running on a flat surface, like man's, did not depend on the speed at which they were running. They concluded that the dog's energy cost of running on a level surface was 1.0 kcal/kg/min, the same

as that of a man. However, they reported the dog's energy cost during uphill running increased at a greater rate than that of a man when the elevation was greater than 12%. With a constant incline, the dogs' oxygen consumption ($\dot{V}O_2$) increased linearly with increasing speed. The $\dot{V}O_2$ in both species increased with increasing work until a maximum value was reached ($\dot{V}O_2$ max). In addition, O_2 extraction from arterial blood increased during more strenuous work (Astrand, 1977; Ordway, Floyd, Longhurst & Mitchell, 1984). The highest $\dot{V}O_2$ measured in dogs by Cerretelli et al. (1964a) was 100 ml O_2/kg/min, which was approximately twice that of an untrained human. Other researchers have reported the untrained dog's $\dot{V}O_2$ max to be 112 ml O_2/kg/min (Ordway et al., 1984) and the trained dog's $\dot{V}O_2$ max to be 146 ml O_2/kg/min (Musch, Haidet, Ordway, Longhurst, & Mitchell, 1985). The average $\dot{V}O_2$ max in some of the best athletes trained in endurance sports was only around 80 ml O_2/kg/min (Astrand, 1977).

In both man and dog, there is increased heat production during exercise that is positively correlated with the intensity of work. There are species differences in heat control mechanisms. With increasing core temperature, a human's skin blood flow and sweat rate increase proportionately. The heat is dissipated by evaporation, radiation and convection (Strauss, 1979). In exercising dogs, panting is the primary mode of heat dissipation. Therefore, lingual blood flow increases during exercise (Fixler, Atkins, Mitchell, & Horwitz, 1976). During panting, the frequency of ventilation increases to rates of 125 breaths per min or higher (Dampney, 1974; Goldberg,Langman, & Taylor, 1981; Jennings, Phillips, Chen, & Sparling, 1973). The air passes in and out of the dead space of the respiratory system quickly, permitting vaporization of

the heat. Another species difference observed during exercise is the dog's ability to significantly increase its hematocrit through splenic contraction. This releases more erythrocytes into the blood and increases the dog's O_2 carrying capacity.

In addition to sharing some physiological similarities, man and dog also share pathophysiological similarities. Some of these are diabetes, respiratory disorders, and cardiovascular disease. Exercise testing has been used to study limitations that may not be apparent at rest, as well as to study any benefits exercise may have for those suffering from such diseases. The dog is afflicted with one particular cardiopulmonary problem that can be related to primary pulmonary hypertension in man. While man does not usually suffer from *Dirofilaria immitis* the results of the disease are similar to those diseases effectuating cor pulmonale in man. Since the dog and man have biochemical and metabolic similarities while running, exercise responses of dogs with *Dirofilaria immitis* may be similar to those of humans with primary pulmonary hypertension.

STATEMENT OF THE PROBLEM

Dogs are used frequently in cardiovascular research. *Dirofilaria immitis* is a serious health problem affecting the cardiovascular and pulmonary systems in many dogs. Reduced work capacity or exercise intolerance is one of the visible signs of canine heartworm disease. While it is well known that this disease lowers work capacity, little information is available on specific physiological responses to incremental treadmill exercise. Characterization of hemodynamic and metabolic responses of the exercising heartworm diseased dog may

help explain the factors contributing to decreased work capacity. In addition, because the damage in the pulmonary vasculature is similar to some found in several human pulmonary diseases, this particular dog may be a model for humans suffering from pulmonary vascular disease or pulmonary hypertension. The purpose of this study was to investigate the effects of heartworm disease on submaximal graded exercise on dogs, with respect to the normal dogs' physiological responses. This information would serve as base data for a comparison of these same responses measured after beta-adrenergic blockade with propranolol.

Review of Literature

Cor Pulmonale

In 1931, Paul White coined the term cor pulmonale as a synonym for pulmonary heart disease, or "cardiac involvement due to pulmonary diseases" (Bhargava, 1973). Increased pulmonary resistance secondary to left heart problems was not included in cor pulmonale's definition (Brill, 1957). Many different definitions of cor pulmonale have been published over the years. To settle the controversy about a definition, the World Health Organization defined cor pulmonale as right ventricular hypertrophy ensuing from diseases affecting the structure or function of the lung, excluding those pulmonary changes resulting from disorders primarily affecting the heart's left side or from congenital heart disease (WHO Technical Series 213, 1961). At this time, most agree that cor pulmonale is a change in right ventricular function (hypertrophy, dilatation, or failure) caused by diseases affecting the lung's structure or function or the pulmonary vasculature, excluding changes occuring as a result of congenital or left heart disease (Ferrer, 1975).

Human diseases causing cor pulmonale fall into two categories (Ferrer, 1975). In the first category are diseases such as chronic obstructive pulmonary disease (COPD)--bronchitis, emphysema, asthma, and fibrocystic diseases. In addition, neuromuscular disorders affecting the respiratory center or muscles, deformities of the chest and some cases of obesity (Pickwickian syndrome) are in the first category. All these diseases are associated with hypoxia, acidosis, and pulmonary vasoconstriction. The second category includes diseases resulting in anatomic obstructive lesions of the pulmonary vascular bed. This latter category includes pulmonary emboli, restrictive pulmonary fibrosis, schistosomiasis, pulmonary arteritides, metastatic lesions, primary pulmonary hypertension, and pulmonary emboli and thrombosis as a result of sickle cell anemia or bacterial endocarditis (Bhargava, 1973; Brill, 1957; Ferrer, 1975; Fishman, 1976). In veterinary medicine, the etiology of cor pulmonale can be attributed to many of the same diseases afflicting man. In addition, heartworm disease would be listed in the second category. It results in thrombosis and emboli obstructing the pulmonary vasculature (Ettinger & Suter, 1970).

The two categories for classifying causes of cor pulmonale may be used to understand the mechanisms producing cor pulmonale. When diseases produce hypoxia, hypercapnia and acidosis, there are circulatory complications. There are vasoconstriction effects which increase pulmonary vascular resistance and decrease the pulmonary vascular bed's capacity. This can result in a pulmonary hypertension. The hypoxia and acidosis stimulate the chemoreceptors, which in turn produce cardiac and respiratory stimulation. The hypoxia and acidosis also bring about a secondary polycythemia and hypervolemia. The already existent pulmonary

hypertension increases. All of these bring about dilatation and hypertrophy of the right ventricle and eventually its failure. In addition to the pulmonary hypertension produced by diseases causing hypoxia, hypercapnia and acidosis, the diseases causing pulmonary vascular anatomic obstructive lesions also produce pulmonary hypertension. This pulmonary hypertension repeatedly dilates the right ventricle, which may hypertrophy. Eventually, there is right heart failure (Ferrer, 1975; Fishman, 1976; Matthay & Berger, 1981). This second mechanism is used to explain the cor pulmonale caused by heartworm disease.

Heartworm Disease

Man has been aware of heartworm disease for at least 300 years. The first report of canine heartworm disease (CHD) in the United States was made by Osborne in 1847. Since that time, there have been numerous reports concerning the incidence, the effects and the victims of *Dirofilaria immitis* (DI).

While DI is most frequently found in the dog, other animals have been afflicted with this parasite. Cats, sea lions, seals, raccoons, muskrats, red and gray foxes, ferrets, otters, bear, deer, horses, orangutans and even man have been hosts for DI (Hirth & Nielson, 1966; Knauer, 1978; Knight, 1977). Most of the information about the life cycle of the heartworm and the incidence and pathophysiology of CHD has been garnered from the research involving DI and the dog. The incidence of CHD is high among the dogs of Louisiana. In a study of Louisiana dogs, Hoskins, Hagsted, Hribernik and Breitschuwerdt (1984) reported that spayed and castrated canines usually had less DI disease

than intact dogs. Medium and large dogs were more prone to suffer from heartworm disease as were the hunting-working breeds. The hunting and working breeds are usually kept outside and therefore have a greater chance of exposure to mosquitoes than pets kept in their owners' homes. Transmission of DI occurs through the mosquito (Kume & Itagski, 1955).

Transmission

There are 60 - 70 out of 3,000 species of mosquitoes capable of developing DI larvae. Approximately 10 - 12 of these species have been recognized as important vectors in the transmission of DI in North America. The most prevalent species are *Culex*, *Aedes* and *Anopheles*. These mosquitoes are the intermediate hosts of the DI larvae (Otto & Jachowski, 1981).

A female mosquito ingests the embryonic microfilariae in a blood meal from an infected animal. Within approximately 10 days, the microfilariae develop from the first stage larvae, L_1, to the infective third stage larvae, L_3. About two weeks after ingesting the DI microfilariae, the mosquito expels the L_3 larvae while biting a host. During the next two to three months, the larvae migrate through the tissues while developing two more stages, L_4 and L_5. As adolescents, the L_5 penetrate the venous circulation and reach the heart. They pass into the pulmonary circulation, causing random emboli in the lungs. The location of the emboli is relative to each lobe's blood flow. The DI mature and push out into the larger, upstream pulmonary arteries and the right ventricle (Knight, 1981). Adult heartworms are usually found in the right atrium, right ventricle, vena cava and pulmonary arteries. However, they have also been found in the caudal aorta and external

iliac arteries, liver, thoracic and abdominal cavities, the ventricles of the brain, and eye. Adult heartworms can live in the dog for five years, during which time they will produce the microfilariae that are found in the blood (Levine, 1974; Knight, 1977; Rawlings, McCall & Lewis, 1978; Stuart, Hoss, Root & Short, 1978; Thrasher, 1965; Winter, 1959).

About one-quarter of the dogs infected with adult heartworms are amicrofilaremic, that is, they do not have circulating microfilariae (Levine, 1974). According to Otto (1978), the amicrofilaremia in occult heartworm disease is found between 10 and 67% of the infected dogs. Occult heartworm disease may be due to prepatent infections, unisexual infections, or drug-induced or immune-mediated adult heartworm sterility (Rawlings, Dawe, McCall, Keith & Prestwood, 1982).

Pathophysiology

The pathophysiology of DI will be affected by the number of heartworms present and the severity of the disease (Jackson, Otto, Bauman, Peacock, Hinrichs & Maltby, 1966). A dog suffering from DI will usually not display any signs during the first six months. Outward signs may not appear until the disease has caused a lot of vascular damage. Some visible signs include a chronic cough, dyspnea and reduced exercise tolerance.

There are some serological changes associated with DI. Eosiniphilia occurs during larvae migration (Rawlings, Prestwood, & Beck, 1980). About six months post-infection, the female adult heartworm releases microfilariae, which causes elevated eosinophil and basophil levels (Rawlings et al., 1978). Barsanti, Kristensen and Drumheller (1977) reported increased beta-globulin concentration and

total serum proteins in microfilaremia. However, Snyder, Liu and Tashjian (1967) found no difference in beta-globulins. Rather, they reported increased gamma-globulin fractions and total serum proteins, as well as smaller albumin and alpha-globulin fractions in microfilaremic dogs. In the same study, they reported greater levels of plasma glucose, serum glutamic pyruvic transaminase (SGPT), eosinophils, leukocytes, and a higher erythrocyte sedimentation rate (ESR). These microfilaremic dogs also displayed lower levels of hematocrit (Hct), hemoglobin (Hb), plasma sodium (Na^+), phosphate, chloride (Cl^-) and bicarbonate (HCO_3^-) than normal dogs. Sharma and Pachauri (1982) found similar changes in microfilaremic dogs' values of serum albumin and globulins, SGPT, Hb, and ESR, but opposite changes in phosphorous and Cl^-. In addition, they reported greater lymphocyte percentages, serum total bilirubin and serum glutamic oxaloacetic transaminase (SGOT) in dogs with DI. Sharma and Pachauri (1982) suggest that the changes in serum bilirubin, globulins and albumins may be attributed to damage of the liver by microfilariae. They also state that the elevations of SGOT and SGPT may indicate pathological changes and cell necrosis of different tissues caused by microfilariae. Calvert and Rawlings (1983) found proteinuria in DI dogs with low serum albumin levels. Usually the proteinuria is mild, but more severe cases associated with a nephrotic syndrome are the result of amyloidosis.

The adult heartworms' presence in the heart causes dilation of the right ventricle and main pulmonary artery. In a normal heart, the stretching of the cardiac fibers can create greater force generated by the contracting cardiac muscle, within physiological limits. This concept is called "heterometric autoregulation" of the heart and was

described by Frank and Starling (Guyton, 1985). However, the force of contraction is also dependent upon the afterload of the heart. In heartworm diseased dogs, increased pulmonary vasoconstriction causes greater pulmonary vascular resistance. The right heart must be pumping against an increased afterload. The dilated right ventricle works harder to produce greater tension for normal right ventricular pressures (Rawlings et al., 1978). As the disease progresses, the Frank-Starling principle is not effective in a dog with heartworms.

The lobar pulmonary arteries also dilate and become tortuous. Endarteritis develops and causes lesions in the vessel walls. This produces stiffer vessels and changes arterial pressures. Dogs with canine heartworm disease (CHD) have greater pulmonary artery pressure, pulmonary wedge pressure, and pulmonary pulse pressure (Olson, Scott, Stoffs, & Robinson, 1982). Blood flow is hindered and circulation time will increase. Cardiac output ($\dot{Q}$) in CHD dogs was 25% less than $\dot{Q}$ in normal dogs. These same CHD dogs also had a smaller blood volume between the pulmonic valves and proximal aorta. In addition, pulmonary vascular and total peripheral resistances were greater in CHD dogs. Pulmonary hypertension develops and causes a reduction in pulmonary collateral circulation (Calvert & Rawlings, 1983; Rawlings et al., 1978). At rest, pulmonary perfusion deficits have been reported in dogs within the first year of contracting DI (Thrall, Badertscher, Lewis & McCall, 1979). This could result in a ventilation to perfusion mismatch and changes in that ratio ($\dot{V}/\dot{Q}$). When $\dot{V}/\dot{Q}$ is low, hypoxia will exist in that lung area. Blood gas analysis revealed relatively low partial pressure of oxygen (PO_2) and high partial pressure of carbon dioxide (PCO_2) levels. While this is the case for some CHD dogs (Rawlings et

al., 1978), abnormal blood gases at rest are not always found (Rawlings, 1982).

Interstitial pneumonitis, an allergic reaction to larvae migration, has been found in dogs with DI (Knight, 1974). The interstitial pneumonitis decreases the lung's resistance and causes alveolar consolidation. As the disease progresses, pulmonary edema also occurs. Additional increments in pulmonary vascular resistance take place and create greater pulmonary hypertension. The right ventricle works harder to maintain flow. Eventually, the right ventricle hypertrophies (Rawlings et al., 1978). This right ventricular hypertrophy is the result of the effects of the development of CHD. The CHD affected the pulmonary vasculature's structure and function to the point of causing the development of cor pulmonale.

In severe DI, the dog may experience syncope, hemoptysis, obstructive fibrosis, anorexia and weight loss, abdominal ascites, limb edema, hypoxemia, renal uremia, glomerulonephritis, and right ventricular and congestive heart failure (Calvert & Rawlings, 1983; Levine, 1974; Rawlings et al., 1978).

Diagnosis

Diagnosis of the disease can usually be made before DI advances to a severe stage. Microfilariae can be detected in the blood from a direct blood smear. If there are few microfilariae, they can be detected after concentration with a Millipore* filter test (Wylie, 1970) or a modified Knott's test (Knight, 1977). In both tests, the stained microfilariae are detected by microscopic investigation. Occult

*Millipore Corp., Bedford, Mass.

heartworm disease may be revealed by an enzyme-linked immunosorbent assay (ELISA), which uses purified adult DI to measure the antibody to the adult heartworm (Grieve, Mika-Johnson, Jacobson, & Cypress, 1981).

Other diagnostic tests help to verify and quantify the severity of CHD. To eliminate the possiblity that another parasite would be causing eosinophilia and basophilia, a fecal floatation should be made. A urinalysis combined with a blood urea nitrogen (BUN) test will be useful in evaluating kidney function. Microfilaremia can cause glomerulonephritis. If nephritis is found, a creatinine determination should be made. Hemoglobinuria may indicate a post caval syndrome in CHD. If bilirubinuria occurs, a hepatic function study should be made. It is possible that microfilaremia causes hepatic venous congestion. Either a SGPT or bromsulphalein (BSP) could provide information on liver function (Calvert & Rawlings, 1983; Hoskins et al., 1984; Knight, 1977; Morgan, 1969).

Blood analysis should include a complete blood count (CBC) with indices and a chemistry profile. Determinations of glucose, SGOT, total proteins and albumin would be part of the profile. These tests will reveal anemia, eosinophilia, basophilia, unusual globulin levels and an indication of other infections. In the advanced stages of CHD, embolisms are common. Therefore the white blood cell (WBC) count and differential will be useful (Calvert & Rawlings, 1983; Hoskins et al., 1984; Knight, 1977; Morgan, 1969). Blood circulation time tests will reveal obstruction to blood flow. The movement of sodium fluorescein (1 cc/9.1 kg) is timed from the injection point, the cephalic vein, to the end point, the oral mucosa. Normal time range is 8 - 12 seconds. The time range in mild CHD is normal or slightly higher. Moderate CHD

range is 12 - 18 seconds. Severe CHD range is greater than 18 seconds (Knauer, 1978; Savell, 1974).

To determine if CHD has caused heart or vascular enlargement, radiographs and electrocardiograms are used. Radiographs reveal enlargement of the right ventricle and main pulmonary artery, and the dense, tortuous branching of the pulmonary arteries. Dorsoventral and left lateral recumbent views are recommended (Jackson, 1969b). Electrocardiography (EKG) can reveal right ventricular hypertrophy. Any three of the following features must be present to diagnose right ventricular hypertrophy by EKG: a positive T wave in lead V_{10}; a mean electrical axis of 110° in the frontal plane; S waves in leads I, II, III, and aVF; a S wave greater than 0.7 mV in lead V_3; R/S ratio less than 0.87 in lead V_3; a S wave greater than 0.05 mV in lead I; and a S wave greater than 0.8 mV in lead V_2 (Rawlings & Lewis, 1978; Tilley, 1979). However, EKG changes do not occur in heartworm disease until pulmonary hypertension exists (Knight, 1977).

A physical examination provides a general evaluation of the CHD patient. This examination would include ausculation of the heart and lungs Jackson, 1969a). In advanced CHD, pulmonary rales and splitting of the second heart sound may be caused by pulmonary hypertension (Knight, 1977).

Exercise

Physiologic animal studies contribute to the understanding of the adaptation of the cardiovascular system to different forms of stress. The body's compensation to the effects of the stress of disease or exercise can be determined. Some exercise studies involving dogs are

limited to limb perfusion in anesthesized dogs. The results of limb exercise studies with canine subjects would be difficult to correlate to normal conditions. Normal conditions involving total body responses to exercise should be used if the results will be compared to humans exercise studies.

The Dog's Responses to Exercise

Exercise increases the workload of the heart, requiring it to increase $\dot{Q}$, in order to supply blood and oxygen to the working muscles. In the dog, $\dot{Q}$ can increase five-fold (Vatner & Pagani, 1976). Cerretelli, Piiper, Mangili, Cuttica and Ricci (1964b) measured $\dot{Q}$, heart rate (HR), stroke volume (SV), and $\dot{V}O_2$ in dogs during submaximal steady-state treadmill exercise. While SV increased slightly (30%), it was reported that the increased HR greatly contributed to the greater $\dot{Q}$. The change in $\dot{Q}$ was complete within one minute after exercise began. The half-time was 20 seconds. As exercise $\dot{Q}$ leveled off, the additional increments in $\dot{V}O_2$ were accomplished with an increase in the arterial-venous oxygen (a-v O_2) difference. Wagner, Horvath, and Dahms (1977) also credited the increased $\dot{Q}$ during submaximal exercise (<50% $\dot{V}O_2$ max) to the rise in HR. During this work, the canine experienced increases in rectal temperature (T_r) and pH, and decreases in venous oxygen (PO_2) and carbon dioxide (PCO_2) tensions, arterial P_{CO_2}, and arterial CO_2 content.

Incremental submaximal exercise stimulated increments in Q, $\dot{V}O_2$, HR and a-v O_2 difference in dogs (Cerretelli et al., 1964b; Wagner et al., 1977). These gains were seen across work, but were significantly higher at greater work intensities. With the onset of exercise, SV significantly rose, then dropped slightly until several workloads later,

when SV increased to the same value recorded at the onset of exercise. Once again, it was stated that the HR played a larger role in the change in $\dot{Q}$ than SV did (Ordway et al., 1984). In this same study, gradual decreases in vascular resistance and no changes in hematocrit (Hct) were noted in the exercising dog. It was suggested that the splenic contraction may have occurred prior to exercise. The dog stores erythrocytes in the spleen. During exercise, splenic contraction produces an increased O_2 carrying capacity in the dog's blood (Vatner, Higgins, Millard & Franklin, 1974).

During mild and moderate treadmill exercise, increments in HR, $\dot{Q}$, SV, and left ventricular systolic blood pressure (SBP) were seen by Fixler et al. (1976). In these exercising dogs, the increased $\dot{Q}$ was primarily mediated by the increased HR. The change in flow to various organs was also measured in this experiment. Flow to the cardiac, diaphragm, intercostal, and gastrocnemius muscles increased significantly above the resting values. Flow to the liver and spleen decreased slightly in mild exercise, but was slightly greater than the resting values during moderate exercise. Flow to the adrenals and tongue were significantly greater, while intestinal flow was significantly lower during both types of exercise. Adjustments in vascular resistance also occurred in exercising dogs. In moderate exercise, estimated vascular resistance dropped in areas of the cardiac, diaphragm, intercostal and gastrocnemius muscles, and in the tongue. Vascular resistance increased in areas of the skin, intestines, brain, kidneys, liver and spleen (Fixler et al., 1976). The changes in resistance and flow to the area of the tongue are essential in the exercising dog so that heat dissipation may occur. Approximately 60% of

the heat is dissipated via the dog's respiratory tract. The remaining 40% of the heat produced is dissipated by radiation and convection (Young, Mosher, Erve & Spector, 1959).

Tipton, Carey, Eastin, and Erickson (1974) developed a submaximal, incremental exercise test for the canine that could be completed by both trained and untrained dogs. They reported that it caused significant increases in HR, mean blood pressure (MBP), coronary blood flow, and Tr. After exercise, Hb, Hct, and pyruvic acid, lactate (La) and free fatty acid (FFA) blood concentrations increased. Glucose concentrations (Glu) decreased.

A maximal exercise test for dogs probably should be classified as an exhaustive exercise test, because a dog will stop running when it becomes tired. Sanders, Werner and Bloor (1976) measured hemodynamic responses in dogs during an exhaustive exercise following five to eight minutes of steady state-exercise at 80% of the animal's maximal HR. The time to exhaustion ranged from 25 to 55 minutes. During the steady-state exercise, the HR, $\dot{Q}$, SV, and aortic pressure rose significantly. The maximal HR and $\dot{Q}$ were significantly greater than the submaximal values. The maximal SV and aortic pressure were approximately the same as those in submaximal exercise. Flow to the liver and intestines decreased with submaximal work, but equalled resting flow in maximal work. Flow to the pancreas and kidney did not change significantly in either type of work.

Other physiological parameters have been studied in maximal treadmill exercise in dogs. Ordway et al. (1984) reported that SV and systemic vascular resistance did not change from the highest submaximal values. The maximal HR, $\dot{Q}$, and $\dot{V}O_2$ were significantly greater, but the

a-v O_2 difference, MABP, and Hct were only slightly higher than the submaximal values. Arterial O_2 content dropped to approximately resting levels. The $\dot{V}O_2$ max values were about the same as those reported for dogs by Cerretelli et al. (1964a), and Young et al. (1959), both of whom used different measurement techniques than Ordway's group. Ordway et al. (1984) analyzed arterial and venous blood samples for O_2 content. They also measured $\dot{Q}$ by dye dilution techniques and calculated $\dot{V}O_2$ with the Fick equation. In the other two studies, $\dot{V}O_2$ was measured through the analysis of expired air (Cerretelli et al., 1964a; Young et al., 1959).

Exercise Responses After Endurance Training

Musch et al. (1985) used the protocol established by Tipton et al. (1974). However, they changed the length of the workloads to four minutes (from three) to facilitate their data collection. The first workload in their study was actually the third workload in Tipton's protocol. Data from the dogs in submaximal exercise were collected before and after two to three months of training. In addition, a maximal treadmill test was administered to the dogs during both test periods. The maximal test consisted of a brief warm-up, followed by increasing the treadmill's speed and elevation until no further change in HR and $\dot{Q}$ could be elicited by the workload, which usually occurred in approximately 8 to 10 minutes.

Musch et al. (1985) found that the HR, SV, $\dot{Q}$, O_2 content, a-v O_2 difference, arterial pressures and systemic vascular resistance responded to submaximal exercise as previously documented. Venous La was measured only at rest and during the fourth workload (6.4 km/hr, 16%

grade). It increased significantly from the resting value (0.82 to 1.21 mMol/L). The posttraining submaximal exercise test revealed that these dogs experienced significant gains in body weight, total blood volume and total plasma volume. A small increase in Hct and skeletal muscle mass were also noted. Training did not produce significant changes in submaximal $\dot{Q}$, $\dot{V}O_2$, O_2 content, a-v O_2 difference, arterial pressures or systemic vascular resistance. Venous La in submaximal exercise was significantly lower than the pretraining level, but not different from the resting value. The training did cause significantly lower HR at each level of submaximal exercise. The SV was significantly greater at rest and across exercise.

Data from the pretraining maximal treadmill test were similar to those of Ordway et al. (1984) and Young et al. (1959). The HR, $\dot{V}O_2$, $\dot{Q}$, a-v O_2 difference, and arterial pressures were greater than those measured in the last workload of the submaximal test. However, SV did not increase. Maximal La was greater. The training period resulted in some significant changes measured in the maximal treadmill test. The $\dot{V}O_2$ max increased by 28%, the maximal $\dot{Q}$ by 27%, a-v O_2 difference by 4%, and systemic vascular resistance decreased by 20%. Venous La and maximal HR were not different from the pretraining values measured in a maximal test. Since maximal HR did not change and there was limited increase in O_2 extraction, most of the improvement in $\dot{V}O_2$ max was caused by SV changes. Maximal SV was much greater than that measured at the last workload of the submaximal test and training increased maximal SV by 26%.

In a similar study, Parsons, Musch, Moore, Haidet and Ordway (1985) used the same protocol to test and train dogs. However, Parsons et al.

(1985) were looking at the biochemical and histochemical skeletal muscle changes induced by training. Consistent with the findings of Musch et al. (1985) in which endurance training produced small changes in maximal O_2 extraction, the dogs in the Parsons et al. (1985) study did not show histochemical or biochemical training effects. Other researchers have also failed to find concurrent skeletal muscle adaptations and increased $\dot{V}O_2$ max in dogs after endurance training (Bove, Hultgren, Ritzer & Carey, 1979; Maxwell, White & Faulkner, 1980; Stone, 1980).

Energy Release During Exercise

When physical activity commences, additional energy is required for the muscles to perform the task. Anaerobic and aerobic energy systems contribute this additional energy in the form of adenosine triphosphate. There is an overlap of contributions of the energy systems. At the onset of exercise, energy is released anaerobically from splitting adenosine triphosphate (ATP). A limited amount of ATP can be replenished anaerobically by three methods. In a creatine phosphate (CP) reaction with adenosine diphosphate (ADP) and hydrogen ions (H^+), the products are ATP and creatine. In a myokinase reaction, two ADPs are combined to form one ATP and one adenosine monophosphate (AMP). The ATP-CP energy system is involved in the first 30 seconds of work. During the next 60 s (after the first 30 s), the ATP-CP energy system and glycolysis contribute additional ATP. Glycolysis is the pathway for energy production, breaking down glucose in the cytoplasm or glycogen in the muscle sarcoplasm. Two (from glucose) or three (from glycogen) ATPs are gained during this process. The end product of glycolysis is La. One and a half min after exercise began, glycolysis and aerobic

metabolism provide the additional ATP for the next 90 s (from 1.5 to 3.0 min). Another source of ATP is available, involving aerobic metabolism and the precursor of La, pyruvate. Pyruvate is transported into the mitochondria where it will be decarboxylated in the Krebs cycle. As blood flow to the contracting muscles increases during exercise, greater amounts of O_2 are transported to the mitochondria, where oxidative phosphorylation will produce more ATP than is possible through anaerobic metabolism. Exercise lasting more than 3 min primarily uses aerobic metabolism as a source of ATP for energy. However, as the intensity of exercise increases, the aerobic metabolism alone is unable to meet energy requirements of exercise. During mild to moderate workloads, blood La levels are approximately the same as resting levels. When exercise intensity exceeds approximately 50% - 60% $\dot{V}O_2$ max, there is an exponential rise in blood La levels in man (Gollnick & Hermansen, 1973; Graham, 1984; Hultman & Sahlin, 1981; Jones & Ehrsam, 1982). The point at which this rise commences has been termed the "anaerobic threshold" (Wasserman, Whipp, Koyal & Beaver, 1973).

Anaerobic Threshold

In 1930, Owles' research concerning La and exercise led him to introduce the concept of a threshold of work above which there is greater La production. In 1964, Wasserman and McIlroy described the exercise onset of anaerobic metabolism as being characterized by "(1) an increase in La in the blood, (2) a decrease in arterial blood HCO_3^- and pH and (3) an increase in the respiratory gas exchange ratio (R)." In 1973, Wasserman et al. defined this anaerobic threshold (AT) as "the level of work or $\dot{V}O_2$ just below that at which metabolic acidosis and

associated changes in gas exchange occur." In 1984 (b), Wasserman defined the AT as "the level of exercise $\dot{V}O_2$ above which aerobic energy production is supplemented by anaerobic mechanisms which results in a significant increase in La". Wasserman's hypothesis is based on the O_2 requirement exceeding O_2 demand in higher work rates with the accompanying gas exchange changes resulting from HCO_3^- buffering La and subsequent acid-base changes.

However, not all researchers believe that muscle hypoxia is the reason for the onset of blood La accumulation (OBLA). Some feel that the rate of La removal becomes different with incremental intensity of exercise, and therefore the cause of OBLA (Gladden, 1984).

Lactate Metabolism

In the tissues and blood, HCO_3^- buffers La. Wasserman and McIlroy (1964) noticed that there was a great decrease in HCO_3^- which began at the OBLA. The HCO_3^- decrement was negatively correlated with the La increment. The buffering of La by HCO_3^- results in an increased production of CO_2, which is eliminated through respiration (Wasserman, 1984a, 1984b). At a point similar to the OBLA, there is an exponential rise in expired ventilation ($\dot{V}_E$) which helps remove the CO_2 and decrease the arterial PCO_2.

The La can be excreted in the sweat and urine. It can also be metabolized by the liver, kidney, heart, and muscles. In each of these organs, La can be converted to pyruvate for use in oxidative phosphorylation in the Krebs cycle. Through the oxidation of La, HCO_3^- is regenerated. The HCO_3^- can cross the cell membrane and enter the plasma, where it is a buffering agent (Gollnick & Hermansen, 1973; Hultman & Sahlin, 1981; Jones & Ehrsam, 1982).

In the kidney and liver, La can be converted to glucose in the Cori cycle (Cori & Cori, 1929). Gluconeogenesis requires a lot of energy and produces H^+. This process is influenced by blood flow and La. Liver La uptake can increase with increasing blood La at rest, during the first minute of exercise and recovery from exercise. During exercise, with the exception of the first minute, liver uptake of La decreases. This is attributed to the reduction of splanchnic blood flow during exercise. The Cori cycle does not have a major role in human exercise La metabolism (Gollnick & Hermansen, 1973; Hultman & Sahlin, 1981; Jones & Ehrsam, 1982).

While human exercise studies have revealed reduced splanchnic blood flow, studies of conscious, exercising dogs have failed to exhibit the same trend (Vatner, 1978). The dogs' mesenteric and renal blood flows did not change in spontaneous exercise outdoors (Van Citters & Franklin, 1969; Vatner, 1978) or in treadmill exercise (Herrick, Grindlay, Baldes & Mann, 1939; Rushmer, Franklin, Van Citters & Smith, 1961). In another study involving steady-state exercising dogs, Dumont, Magrassi, Parent, Stanley, and Chartrand (1984) found significantly lower blood flow in the liver and spleen in exercise. They found blood flow to the intestines and kidneys was not significantly lower than resting values, which contradicts the results of Fixler et al. (1976) in which the dogs' intestinal blood flow was reduced by 40% while exercising moderately for three minutes. Sanders et al. (1976) found that blood flow to the liver decreased in steady-state exercise, but was comparable to resting flow during exhaustive exercise. Blood flow to the kidneys did not change, while spleen blood flow decreased in both forms of exercise. Because research on exercising conscious dogs has not established consistent

findings concerning liver blood flow, it is difficult to ascertain the exact contribution of the Cori cycle to gluconeogenesis during exertion. Depocas, Minaire and Chatonnet (1969) reported the same amount of plasma glucose derived from La during rest and exercise.

Alternative Causes of Increased Blood Lactate

Several other hypotheses on causes of OBLA include fiber recruitment patterns, ammonium (NH_4) accumulation, and enzymatic activity. In incremental exercise, more fast twitch fibers are recruited as work intensifies. Because fast twitch fibers derive their energy primarily from anaerobic metabolism, additional La would be produced (Astrand, 1981). The recruitment of greater numbers of fast twitch fibers and their La production in heavier exercise could be the reason for the OBLA.

At approximately the same time of OBLA, NH_4 has a breakpoint (ABP), followed by an exponential rise. The production of NH_4 is the first part of the purine nucleotide cycle. The increment in NH_4 may stimulate glycolysis (Buono, Clancy & Cook, 1984; Mutch & Banister, 1983). However, NH_4 accumulation may cause a reduction in La removal. Accumulated NH_4 inhibits pyruvate carboxylation (beginning of gluconeogenesis) and pyruvate dehydrogenase (catalyst for pyruvate's conversion to acetyl-CoA). Increased levels of NH_4 also stimulate the production of pyruvate, because it increases phosphofructokinase (PFK) activity (Donovan & Brooks, 1983). After the production of pyruvate, lactate dehydrogenase (LDH) will convert it to La. Thus, there is a clear relationship between increased NH_4 and increased La levels.

Other enzymes affecting La production include LDH and alanine

transaminase. The LDH can act on pyruvate, converting it to La faster than ADP and nicotinamide adenine dinucleotide, reduced (NADH), can take pyruvate into the Krebs cycle. The LDH also acts faster than the alanine transaminase, which converts pyruvate to alanine. Through endurance training, there will be a decrease in LDH activity and an increase in alanine transaminase activity (Holloszy & Coyle, 1984). Therefore, the clearance rate of La is increased (Donovan & Brooks, 1983).

CHAPTER II

Experiment 1

Exercise and Heartworm Disease

One of the signs of CHD is reduced exercise tolerance. A dog with advancing CHD can function normally at rest, but cannot meet the cardiovascular demands of exercise. As $\dot{Q}$ begins to increase in exercise, so does the pulmonary hypertension (Knight, 1968a). In normal dogs, the pulmonary artery pressure (PAP) will increase only after all pulmonary vessels are patent and fully distended (Knight, 1968a). Marshall, Wang, Semler, and Shepherd (1961) measured up to a six-fold increase in the dogs' $\dot{Q}$ without reaching fully distended vessels. The exercise induced increment in PAP in a dog with DI reflects the decreased pulmonary vascular competence. Because of damaged pulmonary vessels, resident adult heartworms, and the resulting development of pulmonary hypertension, the pulmonary collateral circulation is reduced. The combination of the pulmonary hypertension, decreased pulmonary arterial compliance, and the incapability of employing additional arterioles causes the dog's failure to produce the increased $\dot{Q}$ required by exercise (Calvert & Rawlings, 1983, 1985; Rawlings et al., 1978b). An inadequate increase of $\dot{Q}$ during exercise can create a situation in which blood flow is not properly distributed. If the onset of exercise is sudden and of high intensity, the CHD dog may display a slight ataxia or syncope (Knight, 1977).

At rest, total pulmonary vascular resistance (TPUR) in a dog with DI may not be significantly greater than a normal dog's TPUR (Rawlings, 1980). During exercise, a normal, healthy dog's TPUR decreases because of with collateral pulmonary artery recruitment. An exercising CHD dog cannot decrease TPUR as much as a normal, healthy dog (Knight, 1968a). Knight (1968b) studied four CHD dogs during steady-state treadmill exercise, which elicited a three-fold increase in $\dot{Q}$. Two dogs decreased their pulmonary vascular resistance 33 to 38%, another by 29%, and the fourth by only 7%. Compared to a normal dog's TPUR reduction of 52%, it appears that the exercising CHD dog had higher than normal exercise TPUR. Pulmonary hypertension was evident in exercise. The first two dogs, with high normal PAP at rest, became mildly hypertensive in exercise (PAP > 30 mm Hg). The other two dogs had mild hypertension at rest, and had PAP climb to 50 and 70 mm Hg with submaximal exercise. Barger, Richards, Metcalfe, and Gunther (1956) noted a very small increment in PAP accompanying a two to three-fold increase in Q in normal exercising dogs.

Eighteen months after infecting dogs with DI microfilariae, Rawlings (1981) placed a group of these infected dogs with mild pulmonary hypertension into a two and a half month training program. The dogs ran on a treadmill 20 minutes per day for five days per week, which produced an exercise stress comparable to that produced by the protocol developed by Tipton et al. (1974). None of the dogs developed congestive heart failure and their pulmonary hypertension stabilized. Rawlings did not find increased PAP during exercise after a 10 week training period for the CHD dogs.

Some researchers have used isoproterenol (ISP), a non-selective

beta-adrenergic agonist, to simulate exercise responses of the cardiorespiratory system in CHD dogs anesthesized with pentobarbital sodium (Rawlings, 1980; Rawlings, Schaub, Lewis & McCall, 1981). Some of the effects in normal subjects include increases in HR, $\dot{Q}$, and pulmonary vasodilation. ISP also decreases aortic pressure, peripheral vascular resistance, mainly in skeletal muscle beds, and pulmonary vascular resistance, but did not increase PAP in the normal dogs (Rawlings, 1980). In these same dogs, 12 months after DI infection, PAP was significantly higher than pre-infection PAP. In addition, ISP produced even greater PAP values than those post-infection control values. Pulmonary vascular resistance was also greater during control and ISP measurements 12 months post-infection than during pre-infection measurements (Rawlings et al., 1981).

In the CHD exercise trained dogs, Rawlings (1981) also administered ISP 18 months post-infection. Measurements were made before and after the conditioning program. ISP did elicit a higher HR and cardiac index (CI=$\dot{Q}$/body weight), as well as lower pulmonary aortic pressures during each test. Prior to training, the CHD dogs did not experience as large a reduction in pulmonary vascular resistance as normal dogs in a previous study (Rawlings, 1980), when ISP stimulated $\dot{Q}$. After training, these same dogs had a greater reduction in pulmonary vascular resistance. It was hypothesized that these dogs improved pulmonary collateral recruitment with training.

Many aspects of a normal dog's responses to exercise have been studied. There are not as many studies concerning the characteristics of an exercising heartworm-infected dog. Dirofilariasis does decrease exercise tolerance (Rawlings et al., 1978). If the CHD dog does not

have the reserves to open up pulmonary circulation for exercise, does this dog suffer from hypoxemia during work? Can the degree of hypoxemia be correlated to the degree of heartworm infection? If the CHD dog is hypoxemic, will this condition cause higher La levels at rest and/or exercise? Will the CHD dog have a different anaerobic threshold than an apparently healthy dog? The purpose of this study was to characterize the cardiovascular and metabolic responses of moderately heartworm infected dog to submaximal, graded, incremental treadmill exercise.

Methods

Subjects

After screening a group of beagles for DI, eight were selected to participate in this study on the basis of their ability to run on a motorized treadmill without restraint or noxious stimuli, following habituation on the treadmill. The beagles were divided into two groups according to the presence of DI. The control group (N=4) consisted of dogs with negative Millipore* and ELISA tests. The heartworm group (N=4) had a positive Millipore* test. Table 1 lists the group means of age and weight.

*Millipore Corp., Bedford, MA.

Table 1

Biometric Data: Means and Standard Deviations of Age and Weight

GROUP	n	AGE (years)	WEIGHT (kg)
Heartworm	4	2.5 ±.4	11.6 ±1.1
Control	4	2.5 ±.1	11.1 ±2.0

Each dog received a physical examination, which included a blood chemistry profile, complete blood count with indices, fecal flotation, urinalysis, and electrocardiograms. The heartworm group received thoracic radiographs. The group means of the information concerning hemograms, chemical profiles, and urinalysis are in Appendix A.

Physical examination of the dogs revealed no clinical abnormalities, other than typical findings of moderate CHD. Radiographs of the heartworm dogs identified enlargement of the right ventricle and main pulmonary artery. Peripheral pulmonary arteries were distended, with some appearing pruned. Diffuse interstitial infiltrate was present in the lungs. The heartworm disease in these four dogs was classed as moderate. There were no clinical symptoms precluding exercise in any of these dogs.

Animal Care

During the exercise training and experiments, the beagles were housed at the Louisiana State University School of Veterinary Medicine, which is registered and accredited for the care and use of laboratory animals. The standards for animal care established in the National

Institutes of Health (NIH, 1978) documents Principles for the Use of Animals and Guide for the Care and Use of Laboratory Animals were followed. All dogs were fed a mixture of Purina's Field and Farm dry chow and Hill's Prescription Diet food (12.7 kcal/kg/d).

Training

The initial training consisted of short periods in which the dogs adjusted to the starting and stopping of the motor-driven treadmill (Quinton Instruments Model 1849C1). They learned to walk and run at increasing speeds from 2 km/h to 8 km/h without restraint. The exercise period gradually lengthened until the dogs ran for 21 min at 6.4 km/h. The next phase of habituation involved running on inclines from 0 to 20% elevation in increments of 4% at a speed of 6.4 km/h. Following this, the beagles ran the entire submaximal exercise test developed by Tipton et al. (1974) with a Yellow Springs Instrument (YSI) rectal probe (#701) inserted approximately 10 cm past the anal sphincter. During the final phase of preparation for the experiments, the beagles were familiarized with the equipment and procedures that would be used during the study. This last step has been shown to be very important for some research beagles. Beagles trained with restraint, handling, and experimental procedures for 60 days had significantly lower PAP than untrained beagles, whose initial PAP was much higher than anticipated (Bisgard, Orr, Ungerer, and Will, 1972). The training period in the present study took approximately 10 weeks per dog.

Catheterization

In preparation for surgery, the beagles were fasted for at least 12 h to prevent vomiting and aspiration during anesthesia. About .5 h

before surgery, an intramuscular (i.m.) injection of acepromazine (0.25 mg/.45 kg), as a sedative, and atropine (1 ml), to prevent excessive salivation during surgery, was given. For anesthesia, pentobarbital (28.4 mg/kg) was administered to effect intravenously (i.v.) in the cephalic vein. After intubation with a cuffed endotracheal tube to secure a patent airway, the dog was placed in dorsal recumbancy. The neck was shaved and scrubbed with a 1% Betadine* solution. All surgical procedures were performed using sterile techniques and were supervised by a licensed veterinarian.

An incision was made slightly off-center on the ventral side of the neck. The right carotid artery and jugular vein were isolated and cannulated with .040" I.D. x .085" O.D. silastic tubing (Dow Corning Medical Grade #602-201). The tips of the heparinized saline (10,000 u/l) filled catheters terminated at the level of the heart. The tubing had been attached to a woven dacron patch (2 x 2 cm) with silastic medical adhesive (Dow Corning #890). The placement of the catheters was secured by suturing the patch around the vessel. An adaptation of the procedures of Mills and Simmons (1967) was used for chronic implantation of the catheters. The ends of the catheters were tunneled subcutaneously to the dorsal side of the neck and were exteriorized at the base of the neck between the scapulae. A screw clamp was placed on each exteriorized catheter and the ends were temporarily plugged. The catheters were wrapped in a small bundle and secured dorsally to keep the dogs from chewing them.

*Betadine, Purdue Frederick Co., Norwalk, CT.

Postoperative Care

Antibiotics (ampicillin) were administered i.v. immediately after surgery and orally for five days thereafter. The neck was bandaged. The bandaging was changed daily. The sutures were removed 10 days post-surgery. For the duration of the study, the dogs wore cotton stockinette jackets to prevent them from scratching the neck and to keep the bundled catheters out of reach.

The catheters were flushed daily with a small amount of heparinized saline to maintain patency. The dogs' T_r and physical condition were monitored daily.

Preparation for Exercise Testing

While the dog was standing on the treadmill, the end of a YSI probe (#701) was inserted approximately 10 cm in the dog's rectum past the anal sphincter. The position was secured by taping it to the dog's tail. The probe was interfaced with a YSI Telethermometer to measure body temperature. Three-way stopcocks were attached to the ends of the catheters. A pressure transducer (Statham P50), attached to the arterial catheter, was secured to the beagle's chest at the level of the left ventricle and zeroed at that position. The systemic arterial pressure signals were received by a Grass Polygraph (Model 7D).

Data Collection

Before exercise

Pre-exercise HR was monitored through a cardiotachometer, triggered by the pulsatile systemic arterial pressure signals. Pressure and HR were recorded on an 8-channel polygraph (Grass Model 7D). The T_r was recorded and blood samples were drawn. A 1 ml sample of mixed venous

blood was drawn anaerobically in a heparin-treated syringe. The syringe was sealed and placed in an ice-bath until analyzed for blood gas and pH values within one hour of sampling. Simultaneously, 2.5 ml of an anaerobically drawn 3 ml arterial blood sample was immediately transferred to a sodium fluoride (4% NaF) treated tube to inhibit glycolysis and to prevent coagulation. The syringe with the remaining .5 ml of arterial blood was capped and placed on ice until blood gas and pH analyses were done. One ml of the NaF-treated blood was added to 2 ml of chilled 7% perchloric acid for protein precipitation, kept in an ice bath, and later analyzed for La. The remaining NaF-treated blood was analyzed for Glu. An additional 2 ml sample of arterial blood was drawn, from which two microhematocrit tubes were filled. One end of each microhematocrit tube was sealed with clay. Serum was recovered from the remainder of the second arterial sample and used for determination of serum Na^+, K^+, and Cl^-.

During exercise

Each of the seven stages of the exercise test lasted 3 min. After 125 s of each workload, HR, T_r, and arterial pressures were recorded. The mixed venous and arterial blood samples were taken during the last 45 s of each workload. These blood samples were handled as previously described.

Exercise Test

Approximately 8 days after surgery, the dogs underwent their first treadmill test. The 21 min submaximal, incremental test protocol of Tipton et al. (1974) (Table 2) was programmed into the treadmill's automatic controller. After resting data collections, the treadmill was

started at 3.2 km/h and the automatic controls activated. Initially, the speed was 4.8 km.h and the elevation 0%. In the second stage, the speed increased to 6.4 km/h. In each subsequent stage, the incline was raised by 4% until the final stage, during which the dog ran up a 20% elevation at a speed of 6.4 km/h. At the end of the test, the treadmill automatically returned to 0% elevation and 3.2 km/h, before being turned off. After a 10 min recovery period, all instrumentation was removed and the dogs were returned to their housing area. All exercise tests were separated by at least one week.

Table 2

Treadmill Protocol

Stage of Work	Speed (km/h)	Elevation (% grade)	Time (min)
Rest (Pre-exercise)	-	-	-
1	4.8	0	3
2	6.4	0	3
3	6.4	4	3
4	6.4	8	3
5	6.4	12	3
6	6.4	16	3
7	6.4	20	3

Blood Analysis

The arterial blood drawn prior to, and during, each workload was analyzed for Na^+, K^+, Cl^-, Hct, La, Glu, blood gases and pH. The venous

blood was only analyzed for blood gas and pH. After body temperature corrections were made, the blood gas analysis, by a Corning 158 Blood Gas Analyzer, yielded pH, PCO_2, PO_2, HCO_3^-, base excess, and percent O_2 saturation. Hematocrit was calculated by standard procedures after centrifugation (Clay Adams Triac Centrifuge). The K^+ and Na^+ were measured by flame photometry (Beckman KLiNa Flame Photometer). Based on a principle of titration of Cl^- with silver ions, coulometric determination of Cl^- was carried out (Corning 920M Chloride Meter). An enzymatic method described by Sigma (1968) was used to determine La levels. A *B*-D-glucose specific enzymatic analysis to reveal Glu levels was utilized (Worthington Statzyme Glucose Kit). Both La and Glu levels were measured on a spectrophotometer (Bausch and Lomb 2000).

Statistical Analysis

The characterization of the heartworm positive dog in submaximal exercise utilized a two (group) by eight (workload) factorial design. The analysis to determine any differences from the apparently healthy dogs was carried out with an univariate ANOVA with repeated measures on the last factor for each dependent variable. When there were significant workload differences, a Newman Keuls was performed. An alpha level of .05 was selected.

To ascertain any differences heartworm infection might have on the transition to exercise, or at the highest stress of this exercise test, some *t*-tests were done. Paired *t*-tests were made between rest and the first workload values, as well as between rest and the final workload values. Applying a Bonferroni procedure, the alpha level was set at .025 (alpha=.05/2).

Results

ANOVA with a two (groups) by eight (workload) factorial design was used to analyze arterial and venous pH, PCO_2, PO_2, and HCO_3^-, Hct, HR, MABP, T_r, Na^+, K^+, Cl^-, La and Glu. If there were significant workload differences, Newman Keuls tests were applied to determine which workloads differed. When the interaction, group by workload, was significant, each group's least square means were graphed for comparison. Table 3 summarizes the significant effects and interactions of these variables. Table 4 consolidates the results of the paired *t*-tests. Detailed statistical tables are presented in Appendix C. Group means for each of these variables at rest and each stage of exercise are listed in Appendix B.

Table 3

Summary of Significant Effects and Interactions

During Normal Exercise

PARAMETER	GROUP	WORKLOAD	GROUP x WORKLOAD
Arterial Blood			
pH		**	*
PCO_2		**	
PO_2	**		**
HCO_3^-			
Venous Blood			
pH		**	
PCO_2			
PO_2	*	**	
HCO_3^-			
Hct		**	
HR		**	
MABP		**	
Tr		**	
Na^+	*		
K^+		**	
Cl^-		*	*
La		**	
Glu			

* = $p < .05$

** = $p < .01$

Table 4

Summary of Significant Paired t-Tests

During Normal Exercise

Comparison: PARAMETER	Heartworm Dogs		Control Dogs	
	Rest--w-1	Rest--w-7	Rest--w-1	Rest--w-7
Arterial Blood Gas				
pH	*			*
PCO_2	*			
PO_2				
HCO_3^-				
Venous Blood Gas				
pH				
PCO_2				
PO_2				
HCO_3^-				
Hematocrit				
Heart Rate	*	*	*	*
Mean Blood Pressure		*		*
Temperature				*
Sodium				
Potassium			*	*
Chloride				
Lactate				
Glucose				

alpha = .025

* = significant for $-t_{a/2} < p$ or $p > +t_{a/2}$

Electrolytes

The group means for Na^+ ($F_{1,6}$=13.57; p=.0103) were significantly lower in the heartworm dogs than in the control dogs (143.1±0.37 vs 147.1±1.1 mEq/L). The Cl^- levels tended to be lower, while the K^+ levels a little higher. However, the group means for K^+ ($F_{1,6}$=3.55; p=.1085) and Cl^- ($F_{1,6}$=5.58; p=.0561) were not significantly different. The workloads of the submaximal treadmill exercise did not affect the Na^+ levels ($F_{7,42}$=.81; p=.5862), In addition, the paired t-tests for the transition to work (CHD:t_3=.28;p=.6; N:t_3=.3;p=.61) and at the highest level of stress (CHD:t_3=1.31;p=.86; N:t_3=.47;p=.66) did not reveal significant changes. Exercise did affect the K^+ ($F_{7,42}$=17.69; p=.0001) and Cl^- ($F_{7,42}$=2.84; p=.0162) levels. There were no significant group by workload interactions for Na^+ ($F_{7,42}$=1.52; p=.1870) or for K^+ ($F_{7,42}$=1.49; p=.1967). It is interesting to note that the CHD dogs had higher K^+ levels at rest and throughout exercise, while their Na^+ levels were generally lower. The Cl^- group by workload interaction was significant ($F_{7,42}$=2.97; p=.0128) because of different group responses to exercise.

All exercise K^+ were significantly greater than resting K^+. At workload 1 (w 1), there was a large increase in K^+ from the resting K^+ (Figure 1). The remaining changes were smaller increments, significant about every third workload (eg. 1<5, 2<5, 3<6, 4<7) until the last three workloads, in which K^+ values were similar. Paired t-tests for the transition to exercise only approached significance in the CHD dogs (t_3=2.86;p=.968), but were significant in the controls (N:t_3=5.73;p=.995). However, the rate of change for the transition to exercise revealed the CHD dogs had a much greater increment at the onset

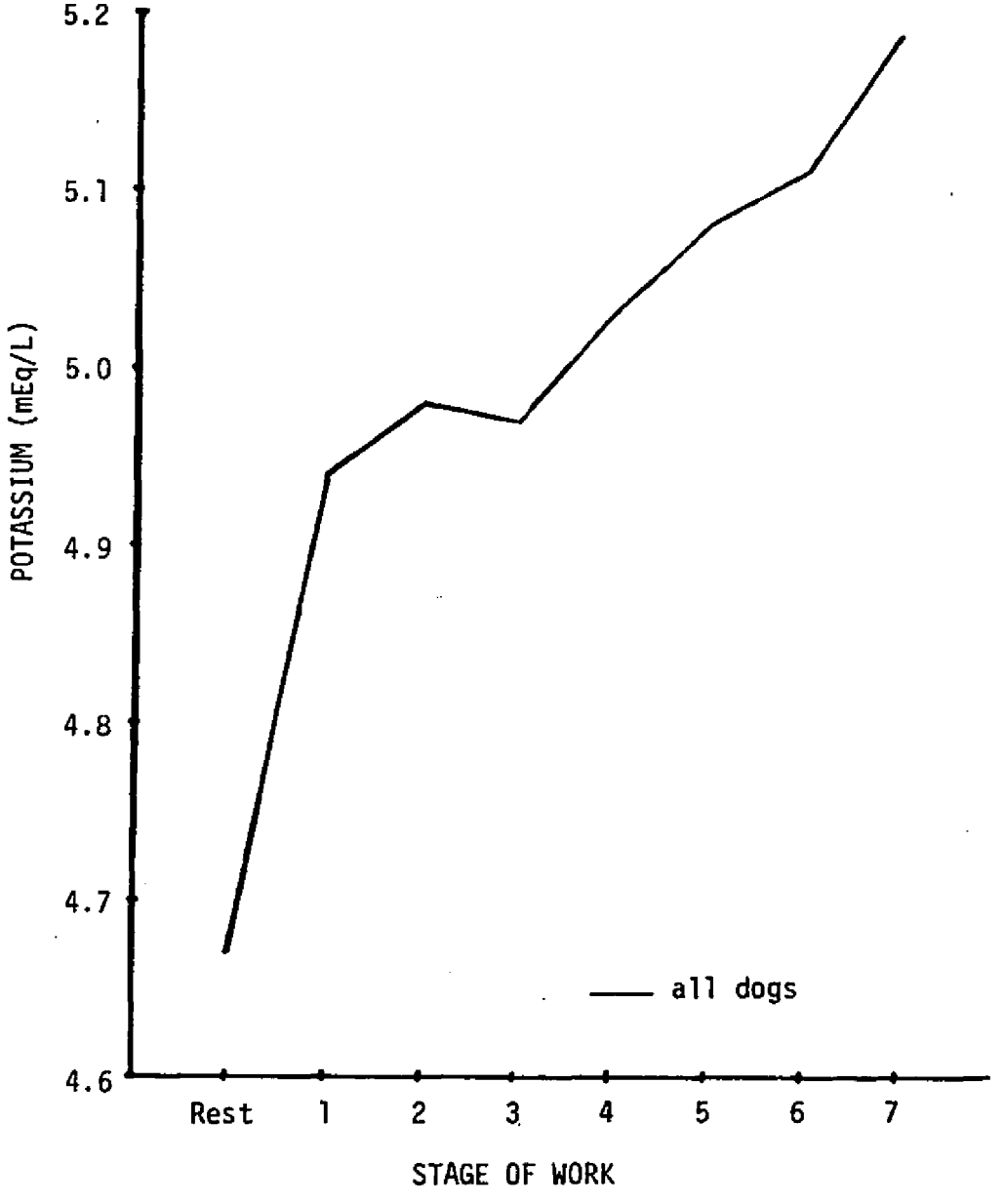

Figure 1. Normal Exercise: Means of Potassium

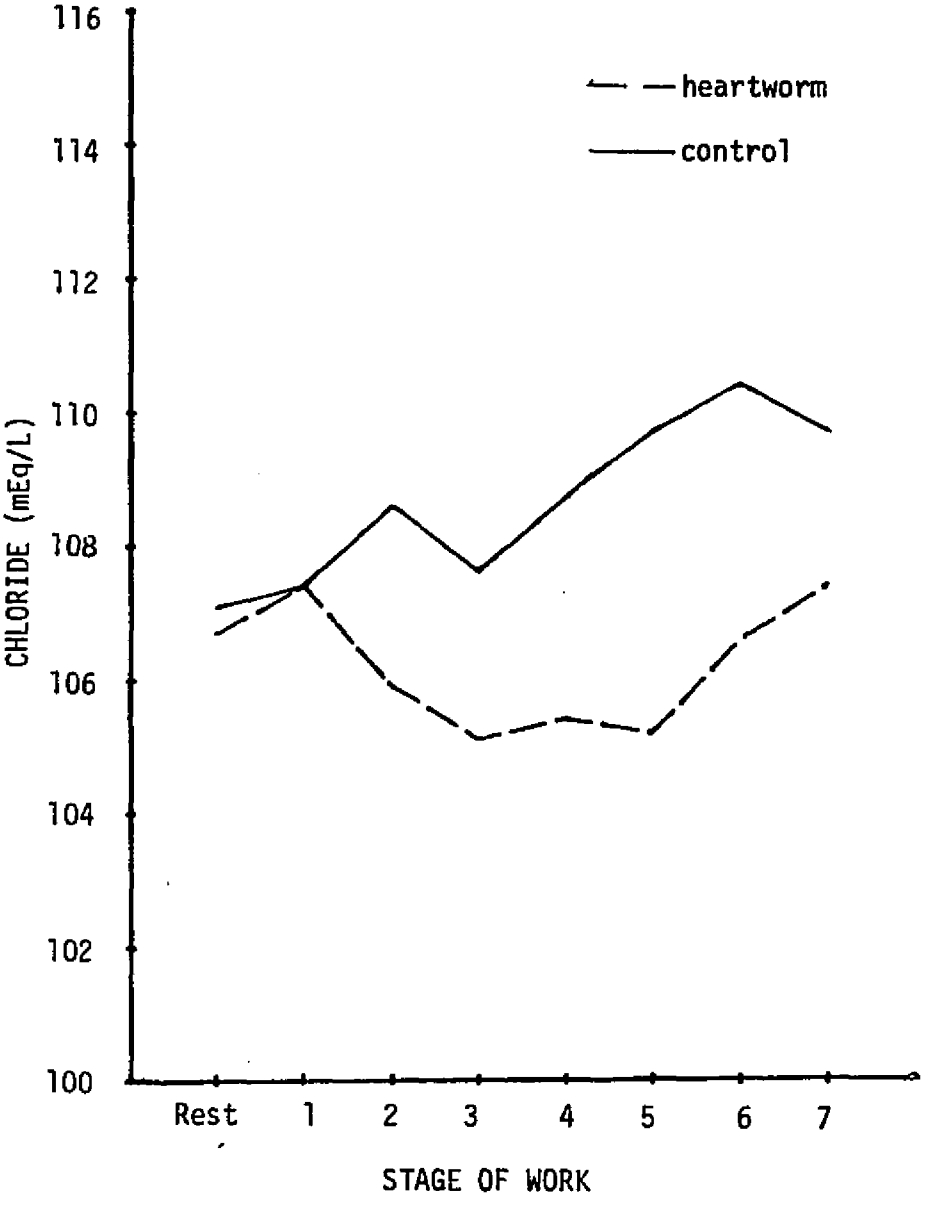

Figure 2. Normal Exercise: Group Means of Chloride

of exercise (7%) than the controls (4%). By the last workload (w 7), their K^+ levels were similar, but the control (N) dogs had a higher gain above resting values (CHD=10% vs N=12%). The paired t-test at the highest level of stress revealed significance for the N dogs (t_3=5.32;p=.994) but not for the CHD dogs (t_3=2.94;p=.97).

Exercise Cl^- levels of the CHD tended to be lower than the N dogs' levels (Figure 2). The CHD and N dogs had similar initial responses to exercise. This transition was not significant for either group (CHD:t_3=.64;p=.715;N:t_3=.29;p=.603). After w 1, the response to exercise followed diverse paths. The CHD dogs' Cl^- levels were significantly lower than N dogs at w 4 through w 6. The CHD dogs did not display a significant change in Cl^- across exercise, while the N dogs had a significant increase above resting and w 1 Cl^- levels at w 6. At the highest level of exercise, neither groups' paired t-test was significant (CHD:t_3=1.53;p=.889; N:t_3=3.48;p=.98).

Glucose

The analysis for glucose only included data from four dogs. There were no group ($F_{1,2}$=.03; p=.8738), workload ($F_{7,14}$=.37; p=.9052), or group by workload ($F_{7,14}$=.83; p=.5813) differences in glucose levels found. The paired t-tests for the transition to exercise (CHD:t_1=1.6;p=.823; N:t_1=.63;p=.678) and at the highest workload (CHD:t_1=.96;p=.744; N:t_1=-.36;p=.391) revealed no significant changes from resting Glu levels.

Lactate

The group means for La ($F_{1,6}$=5.01; p=.0665) were not significantly different. There was a significant workload effect on La

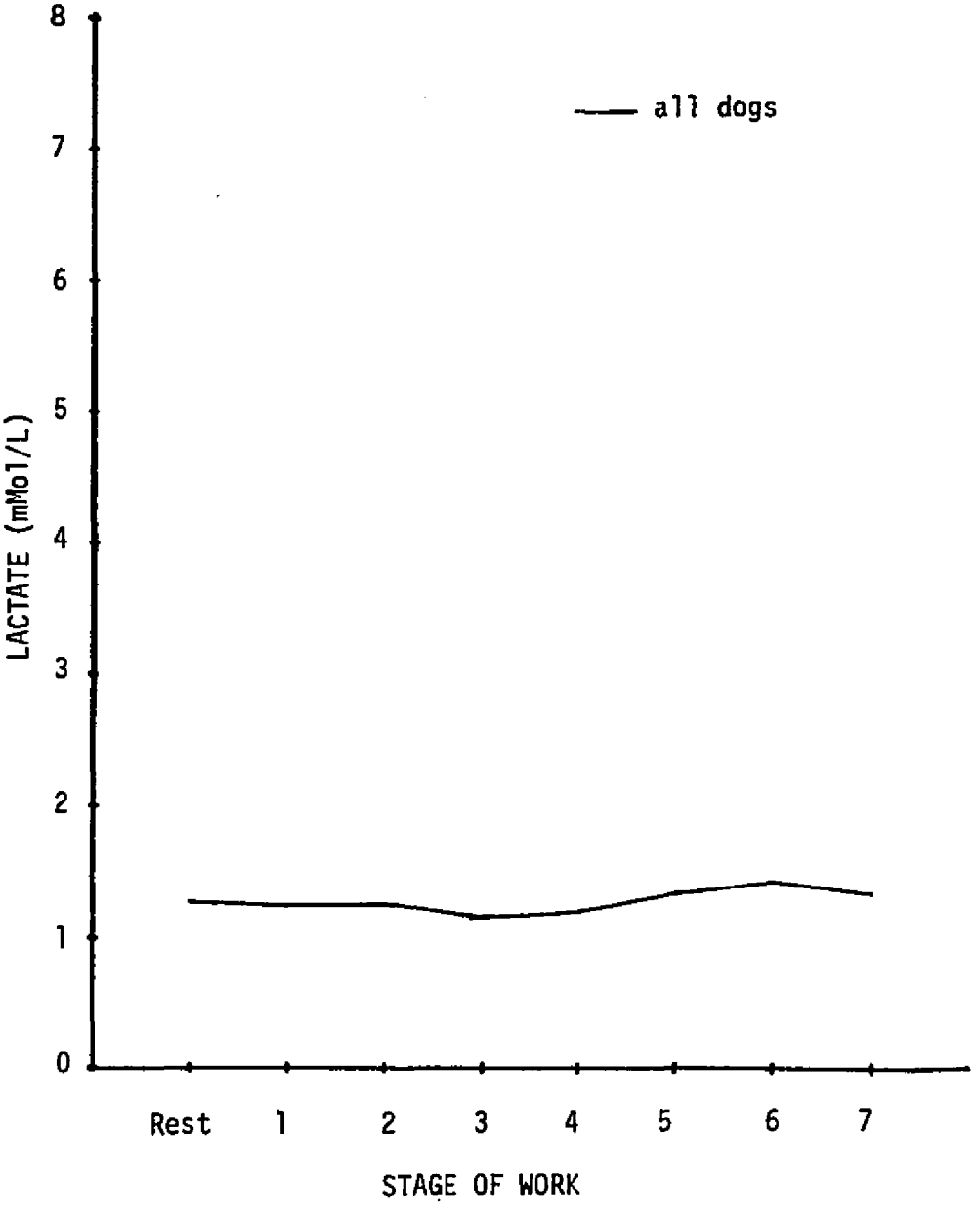

Figure 3. Normal Exercise: Means of Lactate

($F_{7,42}$=4.73; p=.0006). Exercise La fluctuated about the resting level through w 4, after which an upward trend occurred (Figure 3). La at w 7 was significantly greater than all other values, both in exercise and at rest. Because the two groups' La responded similarly across the workloads, there was not a significant group by workload interaction ($F_{7,42}$=1.87; p=.0984). No paired t-test for the onset of exercise revealed significant differences (CHD: t_3=.16;p=.557; N: t_3=-.02;p=.492). In comparing resting La to those at w 7, neither CHD dogs (t_3=1.03; p=.81) nor the N dogs (t_3=2.43;p=.953) disclosed significance. The N dogs exhibited much greater gains from resting La at this level (CHD=13% vs N=58%).

Hematocrit

The resting Hct was significantly lower than all exercise Hct values (Figure 4). Submaximal exercise elicited a significant workload effect ($F_{7,42}$=18.57; p=.0001). There were no significant group ($F_{1,6}$=.08; p=.7866) or group by workload ($F_{7,42}$=1.14; p=.3552) differences in Hct. The paired t-tests from rest to w 1 were not significant (CHD: t^3=1.9;p=.923; N: t_3=1.88;p=.922). Initiation of exercise stimulated the largest Hct increase, which was followed by more gradual increments with each additional workload. The increments seen across work were fairly linear, with significant increases appearing every third workload (eg. 1<4, 2<5, 3<6, and 4<7), with the last three workloads being similar to each other. Comparing data from the highest level of exercise (CHD=41.8±7.3; N=42.9±1.1) with that at rest (CHD=35.3±4.1; N=38.0±2.2), both groups' paired t-tests indicated significant differences (CHD: t_3=3.84;p=.984; N: t_3=3.77;p=.984). The CHD

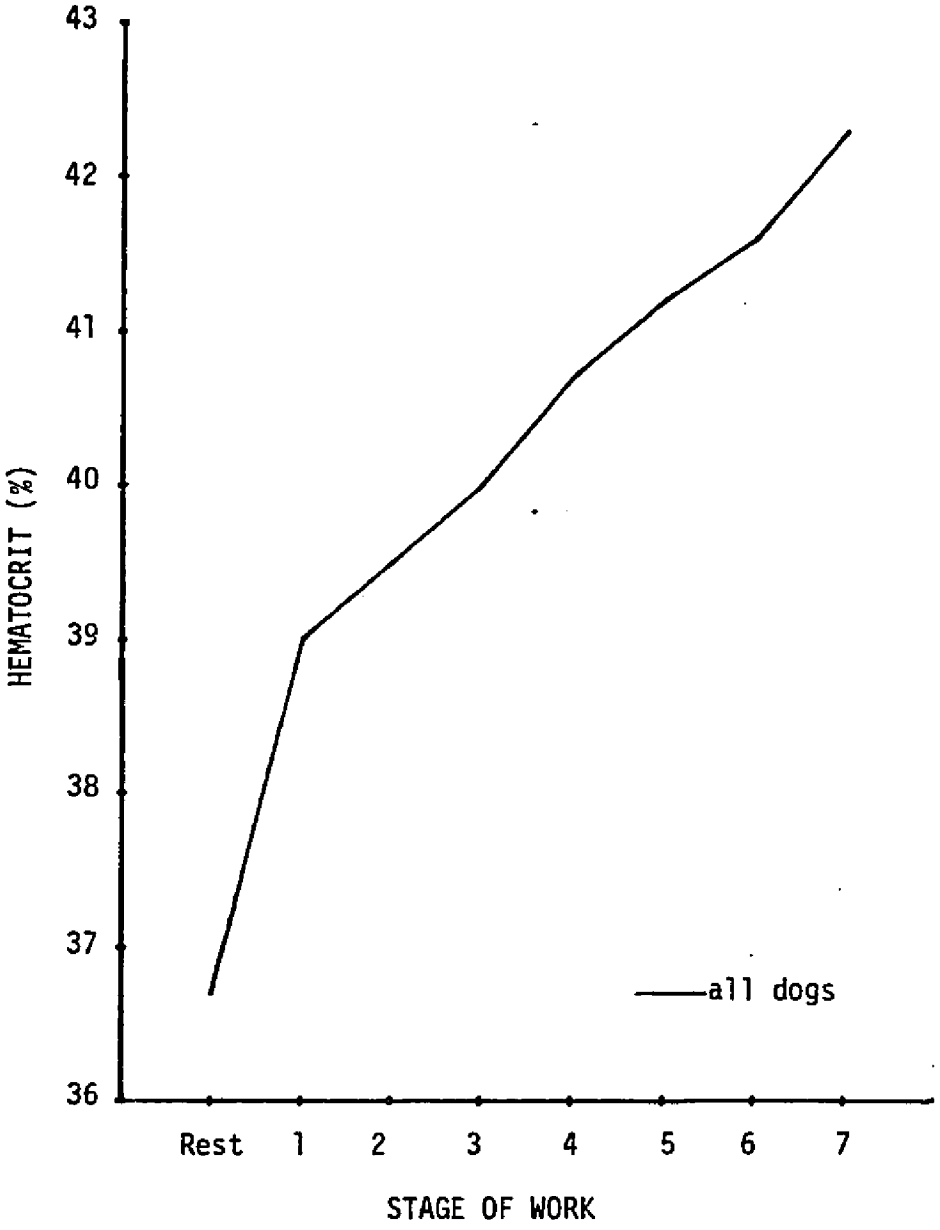

Figure 4. Normal Exercise: Means of Hematocrit

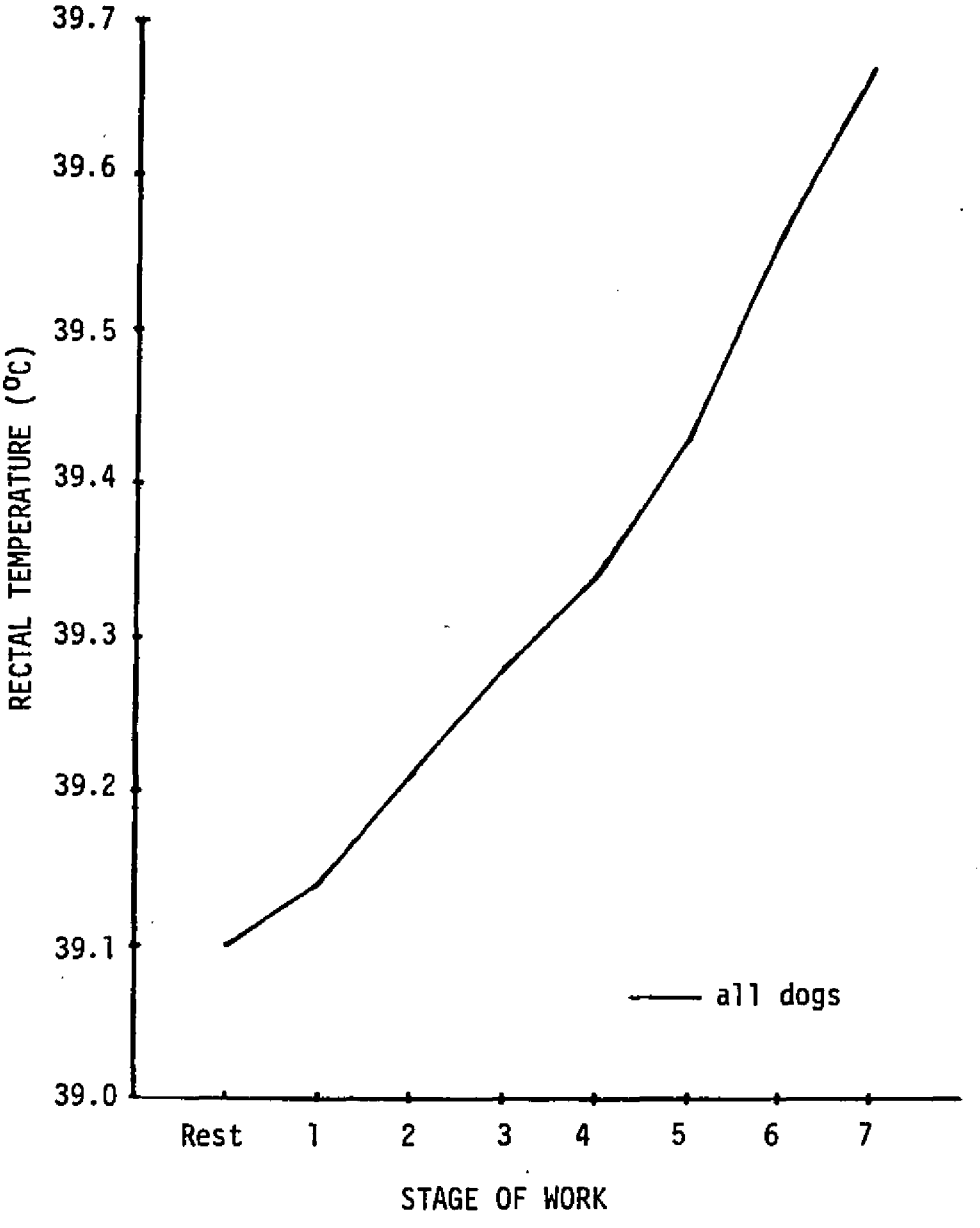

Figure 5. Normal Exercise: Means of Rectal Temperature

dogs had a much greater gain in Hct by the final workload (CHD=18% vs N=13%).

Rectal Temperature

Analysis of T_r did not reveal any group ($F_{1,6}$=.02; p=.8969) or group by workload ($F_{7,42}$=.51; p=.8214) effects. However, exercise did produce a workload effect ($F_{7,42}$=20.99; p=.0001). In general, there was an upward trend from rest throughout exercise observed in T_r (Figure 5). The transition to exercise did not bring about a significant increase from resting T_r in either group (CHD:t_3=2.61;p=.96; N:t_3=1.67;p=.9). Both groups had similar gains at w 1 (CHD=.15% vs N=.1%). The changes noted throughout exercise were smaller in the first four workloads than in the last three workloads. The pattern for significant increases between workloads appeared every third workload, until w 4, after which it was every second workload (eg. R<3, 1<4, 2<5, 3<6, 4<6, and 5<7). In examining differences between rest and the highest level of exercise, only the comparison for the N dogs was significant (CHD:t_3=2.74;p=.964; N:t_3=4.59;p=.991). While the N dogs did have a slightly higher gain (CHD=1.3% vs N=1.6%) over resting levels, the total change in T_r was less than 1° C for both groups.

Heart Rate

No significant differences were found in either the groups' HR ($F_{1,6}$=.10; p=.7670) or in the group by workload interaction of HR ($F_{7,42}$=.56; p=.7835). There was a significant workload effect on the dogs' HR ($F_{7,42}$=18.57; p=.0001). The HR responded rapidly with the beginning of exercise and was moderately augmented with each successive workload (Figure 6). Resting HR was significantly lower than all

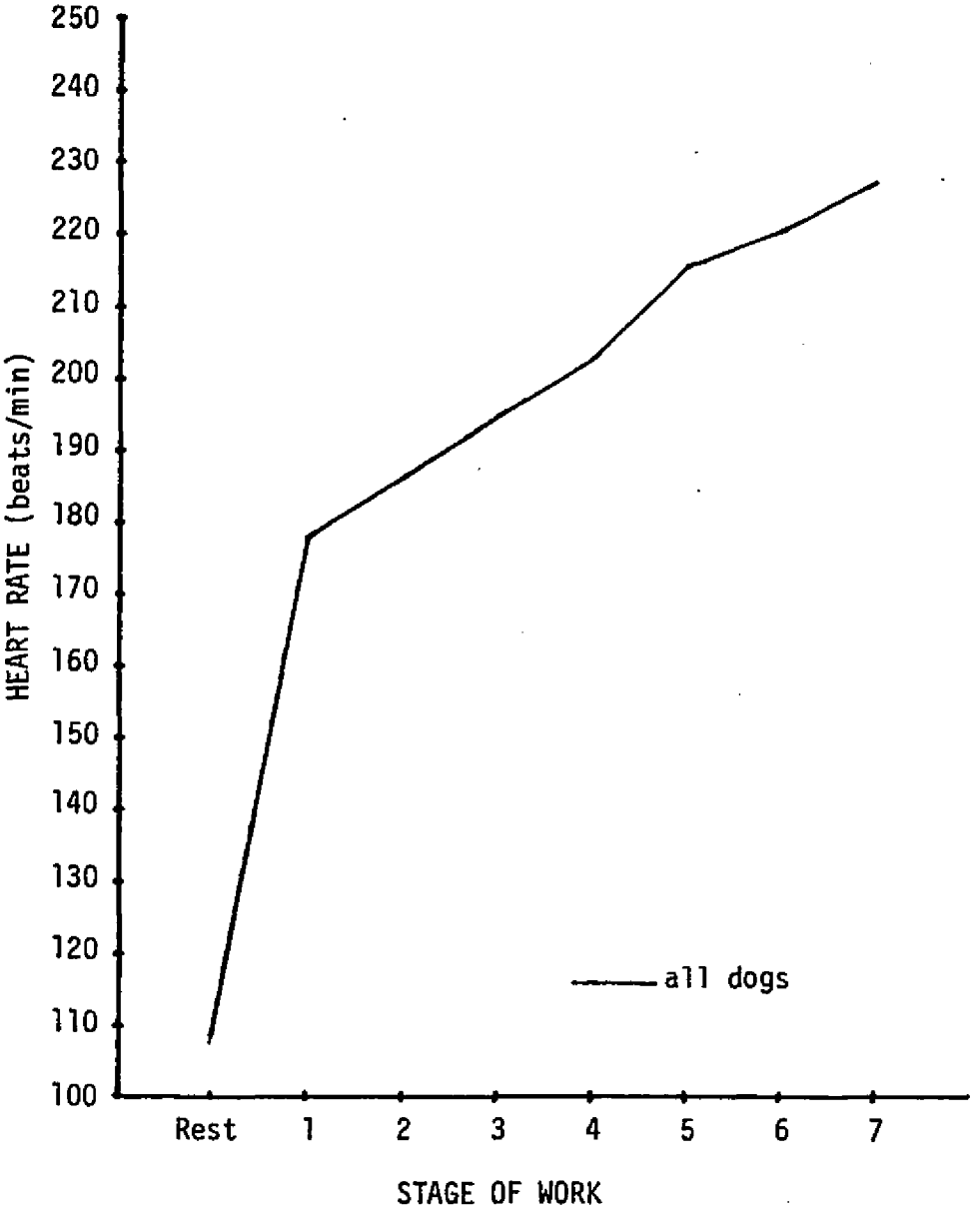

Figure 6. Normal Exercise: Means of Heart Rate

exercise HR. As exercise continued, there was a fairly linear gain in HR. Significant increases in exercise HR occurred every second workload (eg. 1<3, 2<4, 3<5, and 4<6), with no difference among the last three workloads. The heartworm dogs had a slightly lower resting HR (7 bpm), but had a greater increase with the initiation of exercise (CHD=74% vs N=54%). Both groups had a significant paired t-test for the transition to exercise (CHD: t_3=12.61;p=.9995; N: t_3=7.12;p=9971). The paired t-test from rest to the highest workload was significant in both groups (CHD: t_3=7.49;p=.9975; N: t_3=5.55;p=.9942). The CHD dogs' mean HR was slightly higher (15 bpm), and they did have greater gains over the resting HR (CHD=124% vs N=96%).

Mean Arterial Blood Pressure

The MABP analysis included arterial pressure data from seven dogs. The tip of the arterial catheter of one N dog was placed in the left ventricle, therefore arterial pressures were not available for that dog. There were no differences between groups ($F_{1,6}$=.61; p=.4687) or in the group by workload interaction ($F_{7,35}$=1.7; p=.1417) for MABP. There was a significant difference observed in the MABP workload effect ($F_{7,35}$=8.12; p=.0001).

Initiation of exercise brought about a significant increase in the MABP. The transition to exercise was significant (CHD: t_3=12.61;p=.9995; N: t_3=7.12;p=.9971), with the increase in MABP being greater for the CHD dogs (CHD=26% vs N=15%). This rapid rise appeared to be an overshoot, because the MABP dropped a little at w 2 (Figure 7). While resting MABP was significantly lower than all exercise MABPs, none of the exercise values of MABP were statistically different. At the highest level of

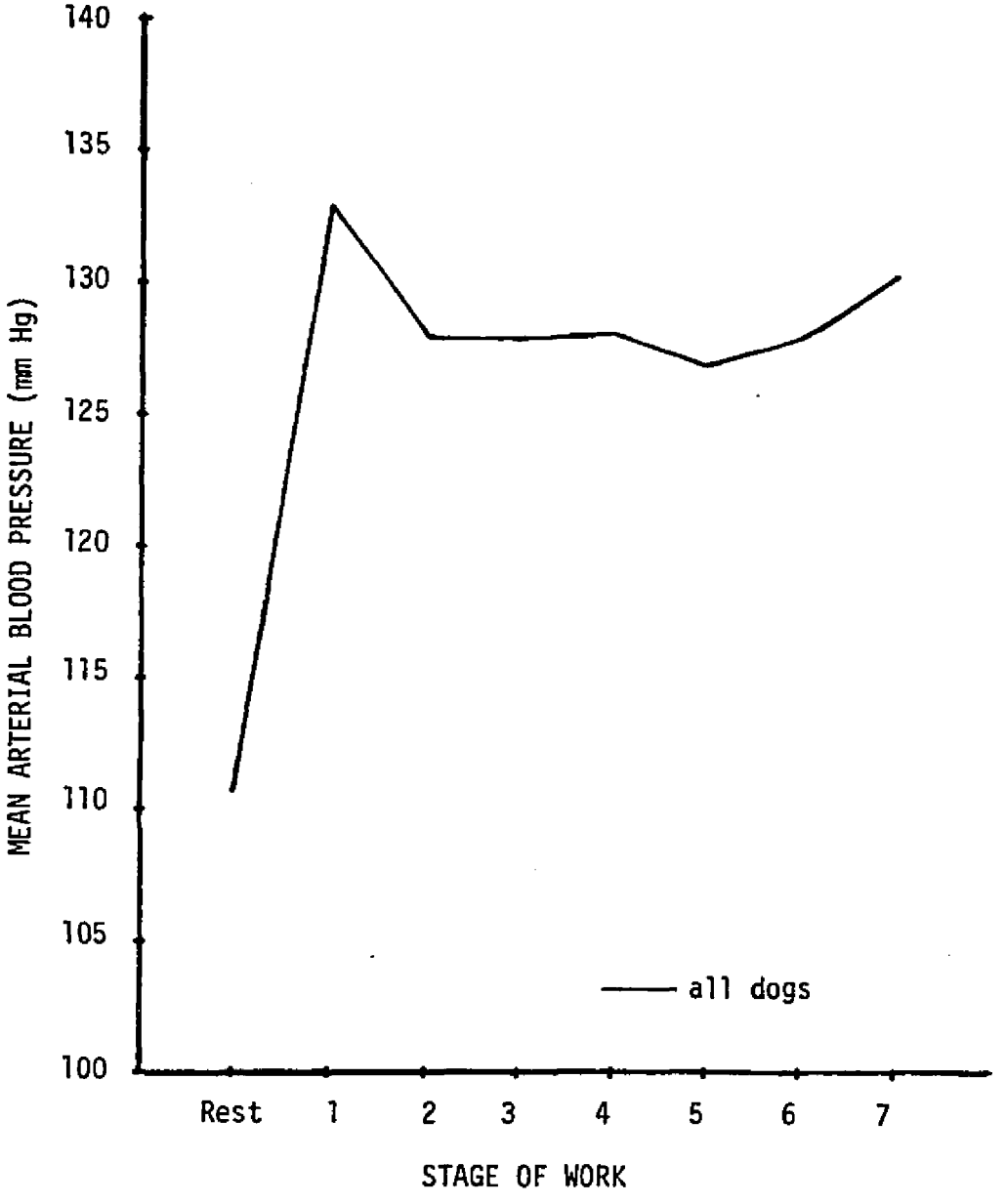

Figure 7. Normal Exercise: Means of Mean Arterial Blood Pressure

exercise, both groups had significant gains in MABP above the resting level (CHD=26% vs N= 9%) (CHD:$\underline{t}_3$=7.49;p=.9975; N:$\underline{t}_3$=5.5;p=9942).

Arterial Blood Gas and pH

The variables analyzed for arterial blood gas and pH included pH, P_aCO_2, P_aO_2, and HCO_3^-. A significant group effect was found for P_aO_2 ($\underline{F}_{1,6}$=22.73; p=.0031), but not for pH ($\underline{F}_{1,6}$=.49; p=.51), P_aCO_2 ($\underline{F}_{1,6}$=2.37; p=.1743), or HCO_3^- ($\underline{F}_{1,6}$=.10; p=.7597). The exercise workloads did not affect P_aO_2 ($\underline{F}_{7,42}$=.79; p=.6) or HCO_3^- ($\underline{F}_{7,42}$=.95; p=.4796). However, there were significant workload effects for pH ($\underline{F}_{7,42}$=8.76; p=.0001) and P_aCO_2 ($\underline{F}_{7,42}$=6.84; p=.0001). Significant group by workloads were noted in pH ($\underline{F}_{7,42}$=2.69; p=.0214) and P_aO_2 ($\underline{F}_{7,42}$=5.03; p=.0003), but not in HCO_3^- ($\underline{F}_{7,42}$=.69; p=.6824) or in P_aCO_2 ($\underline{F}_{7,42}$=2.17; p=.0565).

Exercise produced some dissimilar responses in the two groups' arterial pH (Figure 8). The CHD dogs had a more rapid increment at the onset of exercise (CHD=.65% vs N=.21%) that was significant only in the CHD group (CHD:$\underline{t}_3$=8.28;p=.998; N:$\underline{t}_3$=1.38;p=.869). The CHD dogs maintained an elevated arterial pH through w 5, where there was a slight decrease. The N dogs did not experience a significant increment above resting level until w 6. The paired $\underline{t}$-test for the highest level of exercise was significant in the N dogs (CHD:$\underline{t}_3$=2.78;p=.966; N:$\underline{t}_3$=8.65;p=.998). At w 7, the increase above the resting pH was .54% for the CHD dogs and .59% for the N dogs.

Arterial PCO_2 fell rapidly with the first workload, following which there were no further significant changes (Figure 9). Investigation of the early response to exercise revealed a much larger decrease in the CHD subjects at the onset of exercise (CHD=-11% vs N=-4%). Only the CHD

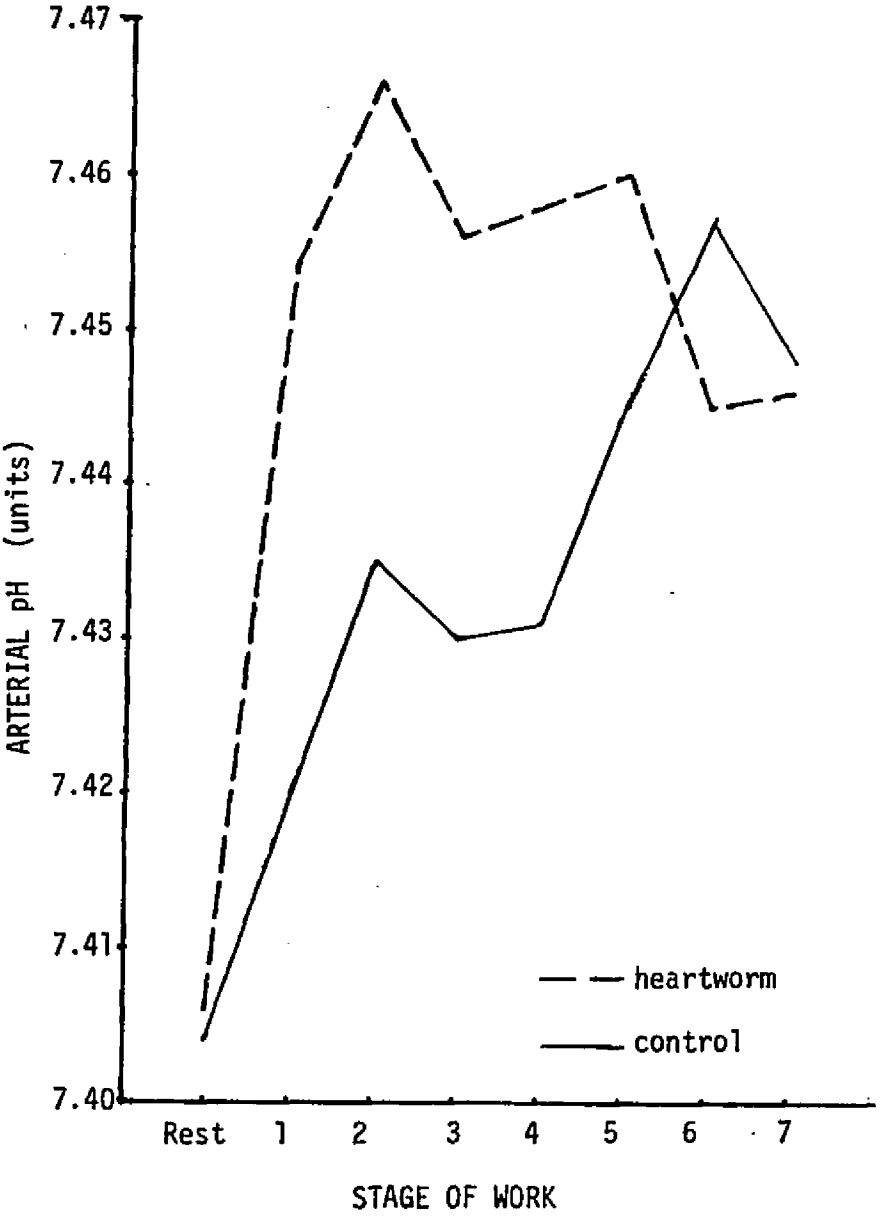

Figure 8. Normal Exercise: Group Means of Arterial pH

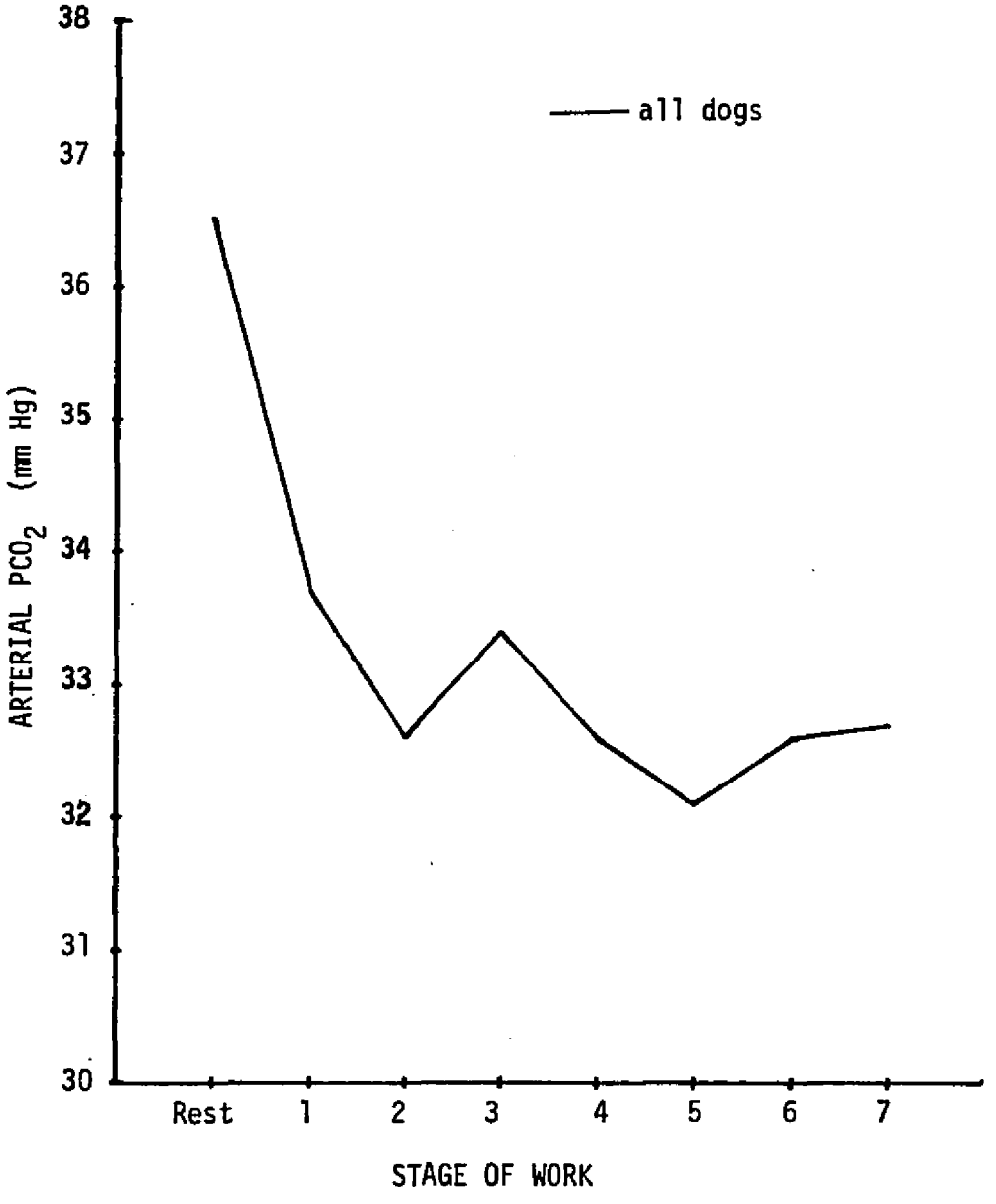

Figure 9. Normal Exercise: Means of Arterial PCO_2

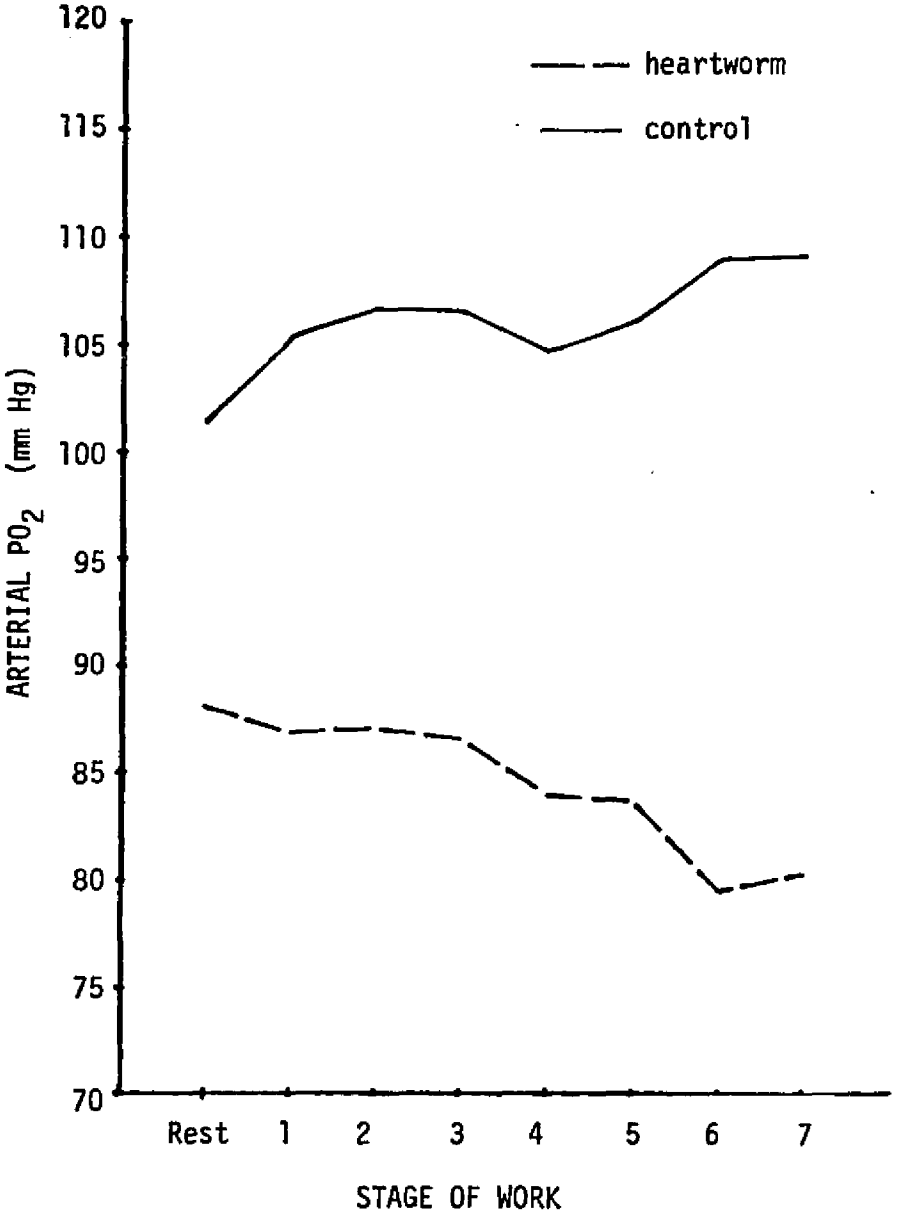

Figure 10. Normal Exercise: Group Means of Arterial PO_2

dogs had a significant change in P_aCO_2 at the onset of exercise (CHD:$\underline{t}_3$=-6.75;p=.003; N:$\underline{t}_3$=-1.07;p=.18). At w 7, the CHD dogs had similar decrements from resting P_aCO_2 and the paired $\underline{t}$-test for this level was not significant (CHD:$\underline{t}_3$=-2.98;p=.029; N:$\underline{t}_3$=-2.88;p=.032).

Unlike P_aCO_2, there were group differences in P_aO_2. The N dogs had significantly higher mean P_aO_2 values at all levels of work as well as at rest (Figure 10). Neither group had significant changes across work. Neither paired $\underline{t}$-test at the onset of exercise (CHD:$\underline{t}_3$=-.42;p=.352; N:$\underline{t}_3$=2.16;p=.9402) nor at the highest level of stress (CHD:$\underline{t}_3$=-1.59; p=.895; N:$\underline{t}_3$=3.47;p=.98) revealed significant changes in P_aO_2 values.

Venous Blood Gas and pH

The variables measured in the arterial blood for blood gas and pH were also measured in the venous blood. Analysis revealed no significant group difference in venous pH ($\underline{F}_{1,6}$=.31; p=.5998), HCO_3^- ($\underline{F}_{1,6}$=.18; p=.6839), or P_vCO_2 ($\underline{F}_{1,6}$=1.06; p=.3428). There was a P_vO_2 ($\underline{F}_{1,6}$=9.84; p=.0201) significant group difference. Exercise produced a significant workload effect in venous pH ($\underline{F}_{7,42}$=4.29; p=.0012) and P_vO_2 ($\underline{F}_{7,42}$=8.69; p=.0001), but not in P_vCO_2 ($\underline{F}_{7,42}$=1.75; p=.1235) or HCO_3^- ($\underline{F}_{7,42}$=.83; p=.5714). There was no significant group by workload interaction found in venous pH ($\underline{F}_{7,42}$=.26; p=.9626), HCO_3^- ($\underline{F}_{7,42}$=.98; p=.4558), P_vO_2 ($\underline{F}_{7,42}$=.23; p=.9771) or P_vCO_2 ($\underline{F}_{7,42}$=1.35; p=.252).

Venous pH did not display a significant increment until w 2 (Figure 11). This increase persisted only through w 4, after which venous pH declined. The comparison of means at the beginning of work was not significant (CHD:$\underline{t}_3$=1.27;p=.85; N:$\underline{t}_3$=.71;p=.74). Neither was the one at the last workload (CHD:$\underline{t}_3$=1.18;p=.84; N:$\underline{t}_3$=.49;p=.67).

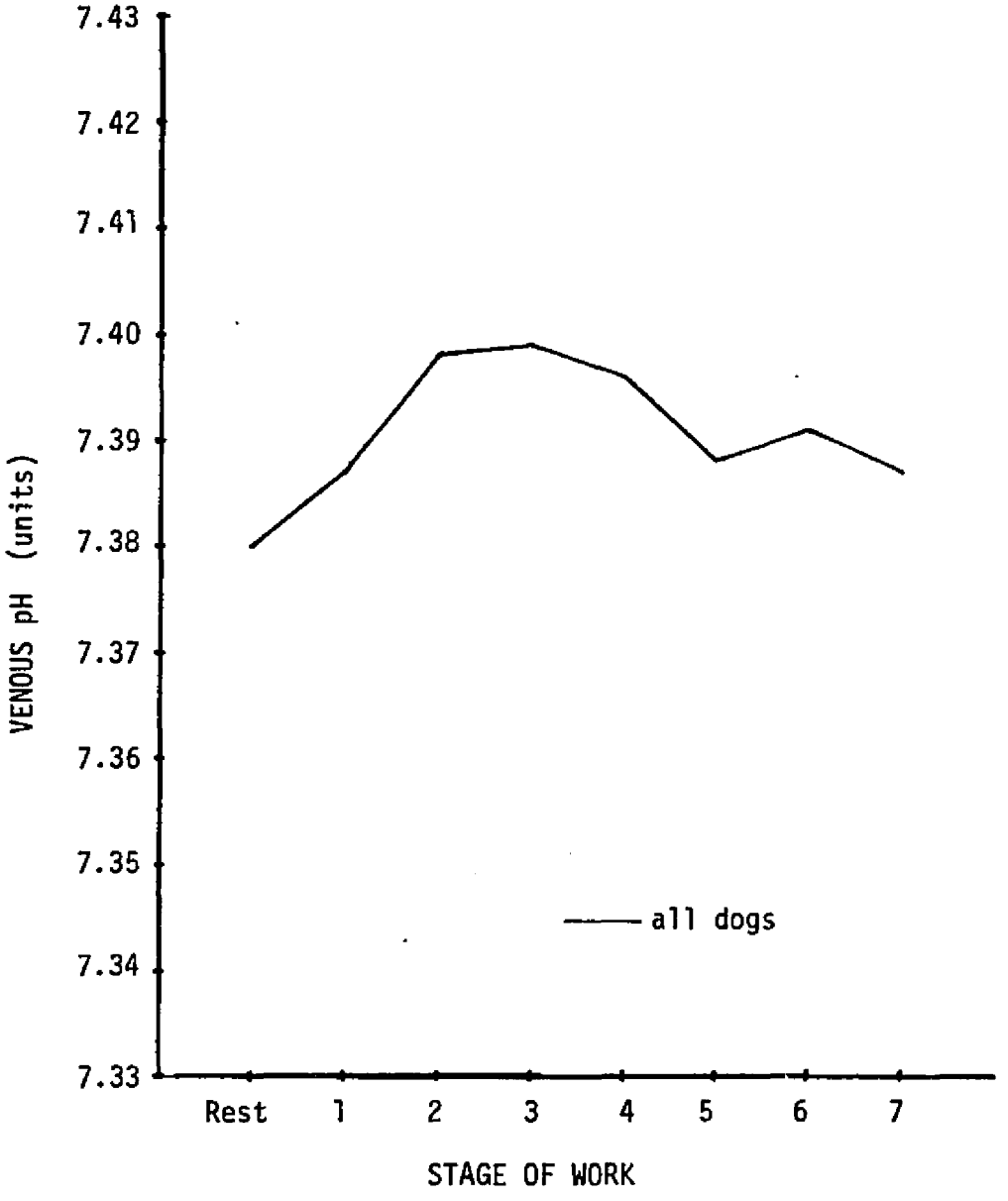

Figure 11. Normal Exercise: Means of Venous pH

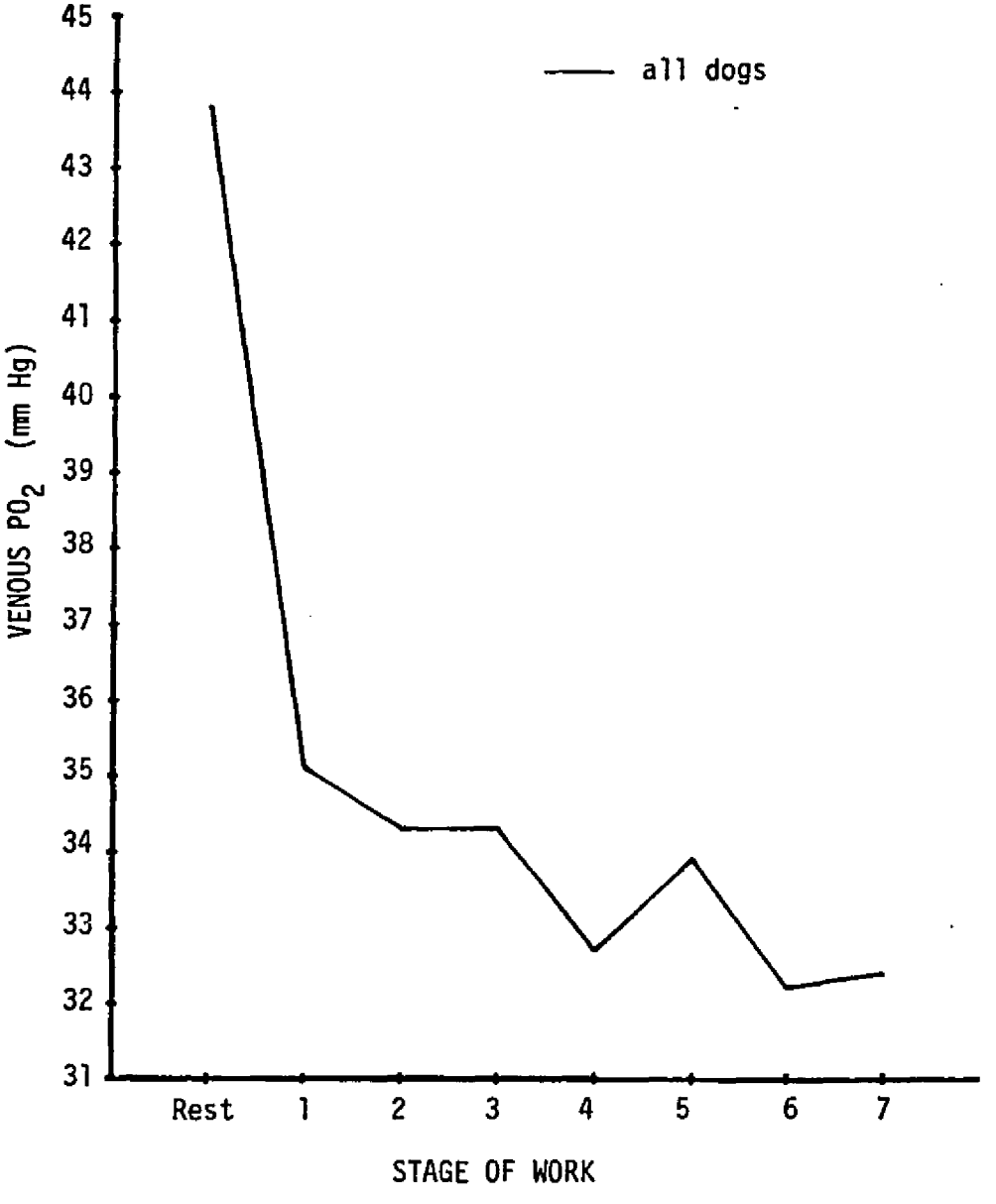

Figure 12. Normal Exercise: Means of Venous PO_2

The beginning of exercise elicited a significant decrease in venous PO_2 (Figure 12). At the onset of exercise, the CHD dogs' P_vO_2 dropped a little more than the N dogs (CHD=-23% vs N=-18%), but the paired t-test was not significant (CHD: t_3=-2.61;p=.04; N: t_3=-1.7;p=.094). As exercise continued, there were no other significant decreases. At w 7, both groups had similar decreases from the resting values (CHD=-25% vs N=-27%), yet only the CHD dogs' paired t-test approached significance for the final workload compared to rest (CHD: t_3=-3.09;p=.027; N: t_3=-2.08;p=.065).

Discussion

Electrolytes

Lower Na^+, K^+, and Cl^- have been reported in CHD dogs by Snyder et al. (1967), however they were not significantly lower. The opposite trend was reported by Sharma and Pachauri (1982), with only Cl^- being significantly greater. Neither of these studies classified the severity of the disease in their subjects. The moderate level of the disease in the dogs in the present study did produce a lower Na^+ and trends to lower Cl^- and higher K^+. The levels of Na^+ and Cl^- in the CHD dogs in this study are in agreement with those in Snyder et al.'s study (1967), but not with those of Sharma and Pachauri (1982). The CHD dogs' K^+ levels in this study follow the trend of Sharma and Pachauri (1982), but are in opposition to those of Snyder et al. (1967). Even though there were differences, all resting and exercise electrolyte values were within the normal range of values for dogs (Current Veterinary Therapy VIII, 1983) and not indicative of physiological abnormalities.

Both K^+ and Na^+ can diffuse across a cell membrane. Active

transport of Na^+ and K^+ across the cell membrane occurs by means of an electrogenic pump and the carrier mechanism of Na/K ATPase. For every every three Na^+ pumped out, two K^+ are pumped back into the cell. In a few areas of the body, such as the renal tubules, Na^+ is also involved in the secondary active transport of glucose and amino acids into the interior of the cell. Various organs, such as the liver, release K^+ via alpha mediated mechanisms. The skeletal muscle take-up of K^+ by membrane-bound Na/K ATPase is $beta_2$ mediated (Staib, Appel, Starey, Lindner, Grotsch, Palm & Grobecker, 1980).

There are many substances that are factors in the humoral regulation of circulation. Some are vasoconstrictors, such as norepinephrine and, to a lesser extent, epinephrine, while some are vasodilators, such as bradykinin, histamine, and ions. An increase in the circulating levels of K^+ decreases the vasomotor tone of smooth muscles through an inhibition of smooth muscle contraction (Kjellmer, 1965). This effect is strengthened by O_2 deficient blood (Skinner & Costin, 1970). A metabolic need and an increased K^+ would contribute to increased flow to that area by dilating arterioles and opening capilllaries. Staib et al. (1980) reported increased catecholamines and K^+ in exercising dogs. Kjellmer (1965) calculated that K^+ released during exercise explained 25 - 65% of the vasodilation during exercise. The norepinephrine would be important in vasoconstriction of vessels to areas not requiring increased flow. The epinephrine helps with vasodilation of skeletal and cardiac muscle vessels requiring an increased flow during exercise. Perhaps the increments in both epinephrine and norepinephrine during the enhanced sympathetic stimulation of exercise act on adrenergic mechanisms to release greater

quantities of K^+ and contribute to the exercise-induced rise in K^+ levels. While the catecholamine levels were not measured in this study, the response has been documented (Staib et al., 1980; & Young, Hintze, & Vatner, 1985). The K^+ did rise significantly during the submaximal exercise test, with the CHD having consistently, but insignificantly higher K^+ levels at rest and each workload.

In addition to stimulating K^+ levels, exercise produced significant Cl^- responses. While not significant, the CHD dogs had a little lower resting Cl^- than the N dogs. Both groups responded similarly at the onset of work, with a small increase. At the same time, the pH increased while P_aCO_2 decreased. These combined initial changes point to a respiratory alkalosis at the onset of exercise, which will be discussed with arterial blood gas changes. With w 2, the groups' Cl^- levels responded differently and the CHD dogs' Cl^- was significantly lower. The CHD dogs' Cl^- decreased until w 5, when it began an upward trend. The N dogs had a general tendancy for an increase in Cl^- across exercise. Their Cl^- was greater than the CHD dogs with the exception of w 1. Analysis of the changes in Cl^- during exercise must consider the role it plays in the buffering processes and CO_2 transport.

The ammonia buffer system removes excess H^+ from the renal tubules and helps regulate the ratio of HCO_3^- to Na^+. The ammonia buffer system uses Cl^-. H_2CO_3 dissociates into H^+ and HCO_3^-, and excess H^+ is excreted in the urine by the combination of Cl^- with ammonium. The HCO_3^- is substituted into the extracellular fluid in place of the Cl^-. In alkalosis, to reduce the pH, the ammonia buffer system removes excess HCO_3^- by combining the HCO_3^- with the ammonium and passing it into the urine. The Cl^- remains behind (Guyton, 1985).

The exchange of HCO_3^- for Cl^- also occurs in CO_2 transport. After an exchange of O_2 and CO_2 between the blood and tissues, the CO_2 in the form of H_2CO_3 dissociates into H^+ and HCO_3^-. The HCO_3^- diffuses out of the erythrocyte into the plasma. To maintain electrical equilibrium, Cl^- diffuses into the cell. This *Hamburger chloride shift* permits the greatest percent of the transported CO_2 to be in the form of HCO_3^- in the blood (70%). In the lungs, the opposite shift occurs to permit excretion of CO_2 (Dejours, 1981).

To ascertain a difference this shift might make in the Cl^-, it might be best to compare the Cl^- in arterial and venous blood. Since the Cl^- in this study was measured only in the arterial blood, this would not be possible. Sejersted, Medbo and Hermansen (1982) felt the *chloride shift* complicated the interpretation of changes during 1 min of maximal exercise and 60 min of recovery. Their two subjects displayed a tendency for Cl^- to increase, just as the N dogs in this study had. However, this study used a longer exercise test that was not maximal. The CHD dogs had a drop in Cl^- except at the onset and in the last 6 min of exercise. The different response suggests an influence of the CHD on Cl^- during moderate exercise. However, because these values were in the normal range and due to the influence of the *chloride shift*, it is difficult to interpret this difference.

Glucose

Snyder et al. (1967) reported higher Glu levels in CHD dogs. In contrast, there was no significant difference in the Glu levels of the two groups in the present study. Heavy exercise causes a decrement in blood Glu levels (Brzezinska & Nazar, 1970). This exercise test

apparently did not stress the beagles in this study enough to cause a decrease in blood Glu levels. These results do not agree with Tipton et al. (1974), who reported a significant decrease in Glu levels immediately after the same type of exercise test. However, due to the small number of subjects' Glu values analyzed (n=4), no trends or differences were revealed.

Lactate

At rest, the CHD dogs had insignificantly higher La levels (1.38±.17 mMol/L) than the N dogs (1.05±.12 mMol/L). Both groups' resting La would be considered normal (1985 Conn's Current Therapy; Musch et al., 1985; Tipton et al., 1974; & Wathen, Rostorfer, Robinson, Newton & Bailie, 1962). Previous dog incremental exercise studies have not measured the La at each workload. Rather, the La has been measured immediately after exercise (Tipton et al., 1974) or during one of the later workloads and at VO_2 max (Musch et al., 1985). These La values are listed in Table 5.

The resting La levels in the beagles were similar to those reported by Tipton et al. (1974), but greater than those of the foxhounds in the Musch et al. study (1985). The beagles in the present study were tested using the protocol developed by Tipton and colleagues (1974). During the last minute of the final workload in the present study, the beagles had a 33% gain in La above resting values. These gains support the data of Tipton et al. (1974) whose normal dogs (32%) and detrained dogs (39%) had similar increments in La measured at the end of the exercise test. The change above resting levels at w 6 in this study (16%) (4 mph, 16%) does not match that reported by Musch et al. (1985) for the untrained foxhounds (48%). The trained dogs' La at the same level of work was not

different from their resting values. Maximal work produced approximately 250% gains in the foxhounds' La. The OBLA in the foxhounds can not be identified with the available data.

Table 5

Exercise Lactate Values

Workload	A	B	C	D	E
Rest: Pre-exercise	1.22 +.21	0.82 +.13	0.77 +.10	1.78 +.66	1.24 +.30
4 mph, 16%	1.41 +.10	1.21 +.17	0.70 +.12	----	----
4 mph, 20%	1.62 +.36	----	----	----	----
Maximal exercise	----	2.83 +.32	2.71 +.41	----	----
Post-exercise	----			2.35 +1.15	1.72 +.21

Values are in mMol/L.
A = present study
B = untrained dogs & C = trained dogs, Musch et al., 1985
D = normal dogs & E = detrained dogs, Tipton et al., 1974

Tracing the La response across incremental exercise in human studies has revealed a fluctuation about resting La levels until a workload demanding about 60-70% $\dot{V}O_2$ max. At that time, there will be an exponential increase in La accompanied by a similar decrease in HCO_3^- (Graham, 1984; Wasserman, 1984b). The mean exercise La values in the present study did fluctuate about the pre-exercise value (1.22$\pm$.10 mMol/l) but did not change until the last workload. However, there was not a concomitant drop in HCO_3^-, which indicates an OBLA might not been

achieved by these dogs when considering just the changes across exercise.

Ordway et al. (1984) utilized the same protocol as the present study and measured $\dot{V}O_2$ at each workload. A similar study by Musch et al. (1985) used an adapted protocol, eliminating the first two workloads and lengthening the remaining workloads to 4 min instead of 3 min. Both groups did use a slightly larger dog, the foxhound. The $\dot{V}O_2$ values for both studies are presented in Table 6.

Table 6

Oxygen Consumption Values in a Submaximal Exercise Test

Workload	Musch et al., 1985		Ordway et al., 1984	
	$\dot{V}O_2$ (ml O_2/min/kg)	% $\dot{V}O_{2max}$	$\dot{V}O_2$ (ml O_2/min/kg)	% $\dot{V}O_{2max}$
Rest: Pre-exercise	12	10.5	16	14.3
w 1: 4.8 km/h: 0%	--		42	37.5
w 2: 6.4 km/h: 0%	--		45	40.2
w 3: 4%	42	36.8	47	42.0
w 4: 8%	50	43.9	51	45.5
w 5: 12%	58	50.9	67	59.8
w 6: 16%	66	57.9	76	67.9
w 7: 20%	79	69.3	93	83.1
Maximal	114	100.0	112	100.0

If foxhounds do have an exponential rise in La about 70% $\dot{V}O_2$ max as observed in humans, one would expect to see such a rise somewhere between w 5 and w 7. The standardized test used for the beagles was the

same one used by Ordway. Granted, there are size differences between foxhounds and beagles, but similar responses in the beagles' $\dot{V}O_2$ should be observed. In a metabolic study on exercising mongrel dogs, Cerretelli et al. (1964a) did not detect an increase in La until the metabolic rate rose to about 280 cal/kg/min. Assuming 1 ml O_2 equals 5 cal, the foxhounds would have achieved that point during w 5. The first significant gain in the present study was observed at w 7. It would be important to know whether there would have been an exponential rise, had further levels of exercise stress been imposed. If that should show a species difference, one might suspect that the uptake of La is probably not hindered by reduced liver flow as seen in humans. In addition, differences in muscle fiber type distribution must be considered in evaluating species differences in La levels during exercise. The anticipated differences in La between the two groups across exercise were not seen.

Hematocrit

At rest, the CHD dogs did have lower Hct (35.3±4.1%) than the N dogs (38.0±2.2%). Lower Hct have been reported in dogs suffering from heartworms (Sharma & Pachauri, 1982; Snyder et al, 1967). These differences seem to have been minimized in exercise, because the Hct values for both groups during exercise were similar and in general agreement with the data of Tipton et al. (1974). In contrast to these results, Ordway et al. (1984) did not find increased Hct, but hypothesized that the increase must have occurred in anticipation of exercise. Initiation of exercise stimulated the largest increase in Hct, which was followed by more gradual increases with each additional workload. An increase in sympathetic stimulation, produced, for example,

with exercise, causes an intense contraction of the spleen, which is alpha mediated. When the dog's spleen contracts in such a manner additional erythrocytes are released into the blood. The Hct response observed in these beagles indicated splenic contraction occurred during this exercise test, which provided increased O_2 carrying capacity for both groups of dogs (Vatner, 1978). Ordway et al. (1984) did not find any changes in Hct after the same submaximal exercise test; however it was thought that those dogs' had splanchnic contraction in anticipation of the exercise test.

Rectal Temperature

Because the exercise test was submaximal, a small change in T_r was anticipated. A small, gradual change in T_r was seen in both groups. The total increase from rest through the highest level of work was less than 1° C. The average ambient temperature in the laboratory was ~21° C, which was 1° C less than a thermoneutral environment (22-25° C). Therefore, there should not have been a problem with heat dissipation during this study. The total increase in the beagles' T_r agreed with the total increase recorded by Tipton et al. (1974).

Heart Rate

At the beginning of exercise, there was a rapid increase in HR. The central nervous system contributes greatly to this response. The predominant regulation of the HR is achieved through the autonomic nervous system, which sends adrenergic and cholinergic impulses to the heart. Exercise tachycardia occurs as the result of an interplay of decreasing vagal tone (decreased parasympathetic inhibition) and increasing sympathetic stimulation. Sympathetic stimulation increases

with neural input and increments in circulating catecholamines (Vatner & Pagani, 1976). The central nervous system can transmit impulses as a subject anticipates exercise, which contributes to rapid inotropic and chronotropic HR adaptations to work. Exercising muscles contribute to HR adjustments during work via afferent nerve fibers. Catecholamines are agonists for the beta-adrenergic and the alpha-adrenergic receptors (Heinsimer & Lefkowitz, 1982), and therefore contribute to the HR adjustments throughout exercise. There is a positive relation between the intensity and duration of exercise and the levels of catecholamines. In exercising dogs, the adrenal medulla is an important source of increased circulating epinephrine and norepinephrine (Peronnet, Nadeau, de Champlain, Magrassi, & Chatrand, 1981).

Approximately 10 weeks had been spent familiarizing the dogs with all the equipment, procedures and personnel involved with the research. This minimized any fear or excitatory responses at the onset of exercise. All measurements were made during the last minute of each workload, so that the dogs achieved steady state for that workload. This avoided any initial transitory overshoot in HR usually seen at the beginning of work or at a new level of work (Donald & Ferguson, 1966). The submaximal exercise test elicited similar responses in both groups of dogs. The HR increased significantly at the onset of exercise, with moderate increments in HR with each subsequent workload.

The HR response to the submaximal exercise test supports the previously reported results of other studies using the same test (Bove et al., 1979; Ordway et al., 1984; & Tipton et al., 1974). But unlike those studies, the HR at the highest workload was about 20 beats per min (bpm) lower than dogs in Ordway et al.'s (1984) and Bove et al.'s

studies (1979). It is highly possible that this happened as a result of "resting" on the collar during the highest workload. During the exercise test, the beagles wore a loose collar and leash in an attempt to protect the pressure transducer from movement if they moved toward the rear of the treadmill. The dogs had to be encouraged to run at the front of the treadmill, instead of dropping back at w 7.

Although the initial response to exercise was typical, the CHD dogs displayed a 20% greater increase at the onset of exercise than the N dogs. Compared to resting HR, the CHD dogs also had a 27% greater gain in HR at the highest stress of the exercise test. Even though not significantly different from the N dogs' HR, the CHD dogs had higher HR at each level of exercise, but a lower resting HR. The difference in Δ % HR was more pronounced in this study than in a group of dogs with chronic right ventricular pressure (RVP) overload (Badke, 1984). Following 9 min of submaximal exercise, dogs with chronic RVP overload exhibited a 6% greater increment in HR than N dogs. In human studies involving cardiovascular performance in patients with COPD (chronic obstructive pulmonary disease), those patients with *cor pulmonale* had slightly higher exercise HR (Khaja & Parker, 1971). A greater percentage of COPD patients displayed abnormal right ventricular ejection fractions during submaximal exercise (Matthay & Berger, 1981) that were not evident at rest. They experienced lower than normal right ventricular output. When a demand for increased $\dot{Q}$ occurs, as in exercise, there is difficulty in achieving the required $\dot{Q}$ through decreased pulmonary resistance and increased pulmonary flow. Pulmonary vascular compliance has decreased and pulmonary vascular resistance has increased. The PAP is greater at rest. Even small changes in $\dot{Q}$ elicit

immediate large PAP increments. To obtain a greater Q, the HR must increase. This is demonstrated in dogs with CHD. After a sympathetic challenge with ISP, dogs with CHD have not been able to decrease the pulmonary resistance as well as N dogs and the higher PAP is magnified (Rawlings, 1981). During exercise, compensations are made to increase $\dot{Q}$. In heartworm disease, the dogs display reduced exercise tolerance because they can not meet the demands for increased $\dot{Q}$ as healthy dogs would. In this study, the higher HR and greater Δ % HR serve to augment $\dot{Q}$.

Mean Arterial Blood Pressure

A pressure gradient from the origin to the end of the vessel is necessary for flow through that vessel. Resistance to flow is another factor in determining flow. The basic relationship between these three factors is $\dot{Q}=\Delta P/R$. The resistance to flow is proportional to the length of the vessel and the viscosity of the fluid. It is also inversely proportional to the fourth power of the radius of the vessel. Vasoconstriction and vasodilation of vessels are means by which the radius of the vessels can be changed. Vasoconstriction would increase resistance to flow, while vasodilation would decrease resistance to flow. When blood flow must be increased during exercise, circulatory adjustments change the caliber of the vessels, which affects the pressure. Alpha adrenergic stimulation of the arteries in areas not involved in exercise causes them to constrict, increasing blood pressure. Alpha adrenergic stimulation of the veins causes constriction, augmenting venous return and therefore $\dot{Q}$. The skeletal muscle and coronary arteries are dilated by beta adrenergic stimulation. This

permits increased flow to these areas.

The dogs' MABP responded rapidly to exercise. The initial response appeared to be a small overshoot, which has been previously reported (Smulyan, Cuddy, Vincent, Kashemsant, & Eich, 1965). Smulyan et al. (1965) hypothesized that an overshoot in HR and MABP at the onset of exercise is due to an overestimation of the neural and circulatory systems of the amount of work to be done. At the onset of exercise, the pressor area of the vasomotor center in the medulla is responsible for the increased arteriolar constriction, peripheral resistance and rise in blood pressure. The vasomotor center controls the sympathetic vasoconstriction nerve stimulation. The vasomotor center receives afferents from arterial baroreceptors, chemoreceptors, the nervous system, and the skeletal muscle fibers. It is believed that the group III and IV skeletal muscle afferents are involved in this exercise pressor reflex (Mitchell, Kaufman, and Iwamoto, 1983).

Throughout exercise, MABP remained elevated. The dogs in two other studies had final exercise MABP comparable to the beagles (Ordway et al, 1984; Musch et al., 1985). Table 7 lists the exercise MABP reported in studies using similar test protocol.

The mean MABP of all the beagles in this study was similar to those reported in the foxhounds (Musch et al., 1985), but a little higher than the MABP duing the first six workloads of the foxhounds in Ordway et al. study (1984). The MABP in w 7 was similar to that in those two studies. However, the dogs in the Tipton et al. study (1974) had mean pressures a little higher at w 7 than dogs in the other studies. The CHD dogs had slightly greater MABP than the N dogs at each workload, which contributed to the higher combined MABP in this study. The CHD dogs

had a greater increment at the onset of exercise than the N dogs, an indication of a larger pressor response to exercise. O'Malley, Venugopalan and Crawford (1985) found an enhanced sensitivity to norepinephrine, a potent vasoconstrictor, in pulmonary artery strips of CHD dogs. Having an increased alpha adrenergic sensitivity, the CHD dogs should exhibit a greater vasoconstriction in exercise, resulting in greater increments of systemic pressure.

Table 7

Mean Arterial Blood Pressures During Submaximal Treadmill Exercie

Workload	H	N	x	M	O	T
Rest: Pre-exercise	109	113	111	119	118	106
w 1: 3mph, 0%	137	129	134	---	114	---
w 2: 4 mph, 0%	134	122	129	---	110	---
w 3: 4%	129	127	128	128	115	---
w 4: 8%	133	123	129	125	116	---
w 5: 12%	131	122	128	124	120	---
w 6: 16%	134	121	129	128	123	---
w 7: 20%	138	123	131	131	128	149

Values are in mm Hg.
Present Study:H=Heartworm Dogs, N=Normal Dogs, x = mean of both groups
M=Musch et al., 1985
O=Ordway et al., 1984
T=Tipton et al., 1974

Blood Gas and pH

With the onset of exercise, ventilation changes. In dogs, there is a rapid response within the first 4 s of exercise, during which time

respiratory frequency and tidal volume increase. This abrupt increment is followed by a slower rise in ventilation and frequency toward a plateau. The time delay of the second phase takes about 20 s. Neural factors are credited with causing the rapid response to exercise, while proprioceptors, chemoreceptors and neural mechanisms contribute to further adjustments (Szlyk, McDonald, Pendergast & Krasney, 1981). During exercise, tidal volume can increase up to five-fold. Functional residual capacity decreases. Blood passes through the lungs more rapidly, which requires the entire capillary length to be involved in gas exchange. The O_2 diffusing capacity and O_2 extraction increase (Wiebel, 1984). In exercise, tissue and venous PCO_2 increase and tissue PO_2 decreases. Changes in the venous blood reflect the tissue changes. During heavy exercise, variations in arterial PCO_2 and PO_2 are not as large (Dejours, 1966).

Unlike the results presented by Wagner et al. (1977), neither group of beagles displayed significant changes in $PvCO_2$. Exercise did provide a small significant increase in venous pH during w 2 through w 4. This response was similar to some previous data (Walthen et al., 1962). The exercise test caused a significant drop in $PaCO_2$ at the onset of exercise, followed by a moderate decline throughout exercise. Arterial pH response was not identical in both groups. The increase was not significant in the N dogs until w 6, whereas the CHD dogs had an immediate significant increase above resting arterial pH that was maintained until w 6. The increase in arterial pH, combined with the decrease in $PaCO_2$ would indicate a respiratory alkalosis during work. These results are in agreement with those of Wagner et al. (1977) and Walthen et al. (1962).

In respiratory alkalosis, there is excessive removal of CO_2 which can be accomplished through hyperventilation. Voluntary hyperventilation favors an increase in PO_2 in the blood and tissues. Exertion increases the ventilatory requirement; this is not a problem for healthy subjects. If there is obstructive lung disease with a $\dot{V}/\dot{Q}$ mismatch, exercise will only increase wasted ventilation and decrease PaO_2. The ventilatory requirement increases and dyspnea occurs with exertion (Brown & Wasserman, 1981). Only the CHD dogs had a significant transitory change from rest to w 1 in arterial pH and PCO_2, which indicates a more difficult adjustment at the onset of exercise compared to the N dogs. Submaximal exercise did not reveal changes in PaO_2, which supports findings of Wagner et al. (1977). Submaximal, incremental exercise increases a-v O_2 diff (Musch et al., 1985; Ordway et al.; 1984). Arterial partial pressures of the dogs in those studies were not reported. The CHD dogs did have significantly lower PaO_2 at rest and each level of exercise. This could be a result of a combination of several factors, such as shunt flow, venous admixture and a mismatch of ventilation and perfusion. The mean $P_{a}o_2$ of both the CHD (85 torr) dogs and the N (106 torr) dogs are supported by P_aO_2 data found in pentobarbital anesthesized CHD (75 torr) dogs and N dogs (101 torr) prior to induced hypoxia (O'Malley, 1986). While the difference in P_aO_2 suggests differences in arterial O_2 content, it would be necessary to measure Hb before determining that difference.

Summary

The CHD dogs had lower Na^+ levels. They also had lower arterial and venous PO_2 values than the N dogs. All dogs displayed similar

exercise responses in Hct, T_r, HR, MABP, K^+, La, and venous pH, which increased during a submaximal incremental treadmill test. There was no indication of an earlier OBLA in the heartworm group. Venous PO_2 and arterial PCO_2 decreased in both groups during work. The CHD dogs had lower exercise Cl^- than the N dogs during the middle of the test. The N dogs had a significant increase in Cl^- towards the end of the test. The CHD dogs' arterial pH rose significantly at the onset of exercise, while the N dogs' rise was delayed until later. The CHD dogs maintained lower arterial PO_2 at rest and in exercise.

All dogs received equal preparation for test yet the heartworm dogs had slightly higher exercise HR, MABP, and K^+. They functioned at rest and exercise with lower PaO_2 than the N dogs. The transition to exercise was apparently a little harder because they had greater increments from rest to the first workload in HR and MABP. They exhibited respiratory alkalosis at the onset of exercise. Perhaps a greater pulmonary resistance and an inability to augment $\dot{Q}$ adequately stimulated "J" receptors in the CHD dogs' lungs, inducing a dyspnea at the onset of exercise. If a difference in adrenergic receptor sensitivity in CHD dogs contributes to an exaggerated exercise pressor response at the onset of exercise, future exercise studies should investigate the effect of adrenergic blockade in CHD dogs.

CHAPTER III

Experiment 2

Beta Blockade in the Exercising Heartworm Infected Dog

Propranolol is a short-acting, non-selective, beta-adrenergic antagonist. The dose for adrenolytic beta blocking in dogs is 2 mg/kg i.v. (Barnes & Etherington, 1975). This blockade's effects are most noticeable during periods of increased sympathetic tone, such as in exercise. Exercise performance would be affected because of the drug's action on the heart, vasculature and lungs. Propranolol decreases HR, $\dot{Q}$, arterial blood pressure, and atrioventricular conduction velocity. It can allow increased peripheral vascular resistance and bronchoconstriction by removing the sympathetic arm of autonomic control (Muir & Sams, 1984). Propranolol also interferes with the interaction of catecholamines with beta-adrenoceptive sites through competitive inhibition (Mylecharane & Raper, 1973). Metabolic effects of beta-adrenergic blockade include greatly decreased resting FFA and La, while Glu fluctuates insignificantly above and then below normal levels (Brzezinska & Nazar, 1970).

Hepatic glycogenolysis is mediated by beta-adrenergic receptors in the dog (Hornbrook, 1970). The adrenergic system also plays an important regulatory role in muscle metabolism (Brzezinska and Nazar, 1970). The rate of glycogenolysis in the dog's exercising muscle is increased by epinephrine (Issekutz, 1978), circulating levels increasing in

proportion to the intensity and length of exercise (Astrand, 1977). Research with the exercising dog has revealed that metabolism is decreased by beta-adrenergic blockade.

In both short, intense exercise and prolonged, moderate exercise, dogs receiving propranolol displayed smaller increases in La and pyruvate (Brzezinska & Nazar, 1970). Beta-blockade also decreased the exercise lactate/pyruvate (L/P) ratio and level of circulating FFA. The changes in circulating FFA during exercise could promote La's oxygenation and might be an indication of inhibited lipolysis in adipose tissue. While Glu was not affected in normal or beta-blocked, short, high intensity exercise, it was affected during prolonged, moderate work in dogs. The exercising dogs experienced decreasing Glu levels and hypoglycemia after about 120 min. After propranolol, the Glu was much lower and the onset of hypoglycemia was more rapid.

Cronin (1967) and Issekutz (1978) both reported decreased levels of La in beta-adrenergic blocked dogs exercising at short durations (varied speeds) and long durations, respectively. Issekutz measured a propranolol-curtailed La production, which was attributed to a blockade of extrahepatic glycogenolysis. He additionally found a restrained exercise-induced rise of FFA and an incremented glucose turnover rate after beta-blockade. Barnard and Foss (1969) exercised their dogs at higher work rates and reported peak La values after propranolol being lower than those without blocking.

The hemodynamic effects of beta-adrenergic blockade in exercising dogs was studied by Bassenge, Kucharczyk, Holtz, and Stoian (1972). In the control group of their study, coronary flow (CF), HR, SV, and MABP responded rapidly. Propranolol delayed response times and adaptation to

exercise. It also eliminated the overshoot in HR and CF observed in the beginning of unblocked steady state exercise. In mild exercise, Bassenge et al. (1972) reported that propranolol enhanced the SV, which offset the lowered HR so that $\dot{Q}$ was maintained at a level comparable to the non-blocked $\dot{Q}$. This was unlike a finding of other studies in which mild exercise after beta blockade significantly reduced SV (Heyndrickx, Pannier, Muylaert, Mabilde, & Leusen, 1980; Horowitz, Atkins, & Leshin, 1974). Bassenge et al. (1972) also found greater differences in $\dot{Q}$ at higher workloads. In steady state exercise (Bassenge et al.,1972), the HR decreased by 15%, $\dot{Q}$ by 25%, MABP by 8%, and coronary flow by 26% after beta blockade.

In all levels of treadmill exercise (mild, moderate, and severe), several researchers (Heyndrickx et al., 1980; Horowitz et al., 1974) found that beta-blockade in exercising dogs significantly lowered HR, SV, $\dot{Q}$, MABP, and myocardial force development (dp/dt). Beta-adrenergic blockade caused a significant increase above control values in a-v O_2 difference during mild and moderate exercise. In addition, propranolol decreased myocardial $\dot{V}O_2$ (Heyndrickx et al., 1980). While beta-blockade tended to decrease whole body $\dot{V}O_2$, it was not significantly lower than control exercise $\dot{V}O_2$ until more strenuous workloads (Barnard & Foss, 1969; Cain, 1970; Cronin, 1967).

Regional blood flow in the dog was measured at rest and during steady-state exercise before and after propranolol (Dumont et al., 1984). At rest, flow to the liver and spleen following propranolol were approximately one-half the value measured without beta-adrenergic blockade. However, during exercise after beta-adrenergic blockade, the flow to the liver and spleen were not significantly different from beta

blocked resting values. During beta blocked exercise, spleen flow was not different from the values found in the exercise without propranolol, but liver flow was slightly lower than the control exercise liver flow. Blood flow to areas of the heart (right ventricle, septum, left ventricular subendocardium and subepicardium) during normal exercise increased greatly above resting values. After beta-adrenergic blockade, blood flow to these areas tended to decrease a little (not significantly) at rest and was significantly less during exercise than the unblocked flow during exercise. However, if myocardial ischemia was present, the decrease in resting flow to the ischemic area of the subendocardium was not as great after administration of propranolol (Vatner, Baig, Manders, Ochs, & Pagani, 1977).

Dumont et al. (1984) also measured local vascular resistance in the dog at rest and during exercise before and after propranolol. Under normal conditions, local vascular resistance dropped significantly in the heart, diaphragm, and triceps during exercise. With beta-adrenergic blockade, vascular resistance in exercise was still lower than resting values but was much greater than the resistance during normal exercise. After propranolol, vascular resistance in the liver and spleen was almost triple the normal resting value. In these two areas, the resistance during exercise was similar to the blocked resting values, but much greater than the normal exercise conditions.

Staib, et al. (1980) hypothesized that increased peripheral resistance after beta-blockade would be the result of increased circulating catecholamines. Normally, there are higher levels of circulating catecholamines during and after exercise. After receiving propranolol, the exercising dogs had even greater catecholamine levels

than control exercise (norepinephrine) and post-exercise values (norepinephrine and epinephrine). In addition, the enhanced catecholamine levels persisted for a longer time after beta-blocked exercise. While propranolol blocked the release of norepinephrine at rest, beta-blocked exercise stimulated sympathetic nerve endings and the adrenals to release catecholamines. This release continued into the recovery period.

Accompanying the enhanced catecholamines, Staib et al. (1980) also found increased exercise plasma K^+ in the dogs receiving propranolol. These increments were significantly greater than the normal elevation of plasma K^+ in exercising dogs. Following unblocked exercise, the plasma K^+ quickly returned to resting levels. However, in beta-blocked exercise, the elevated plasma K^+ levels prevailed during a 60 min post-exercise recovery period. Similar behavior of plasma K^+ results was revealed in beta-blocked dogs exercised by Carlsson, Fellenius, Lundborg and Svensson (1978). Both groups attributed these differences to interference of beta-adrenergic control mechanisms. Carlsson et al. (1978) thought the potentiation of the K^+ increase during beta blocked exercise might be the result of blocking the β_1 adrenergic receptors, while the delayed return to normal resting values after beta blocked exercise was caused by blocking the β_2 adrenergic receptors. Staib's group also thought that alpha-adrenergic activity was enhanced, causing additional release of K^+ from the liver and muscle. The hyperkalemia in beta-blocked exercise could contribute to the muscle fatigue and decreased exercise performance noted in some studies (Fellenius, 1983).

Tolerance to exercise after propranolol should be reduced. The purpose of this experiment will be to answer several questions. How

will the propranolol affect a dog with CHD that already has a degree of exercise intolerance? In the incremental treadmill test, how will beta-adrenergic blockade affect La and the OBLA in the dog? Perhaps the CHD dogs, whose P_aO_2 are lower than the control dogs in this study, will have a La accumulation during beta blocked exercise. By reducing Q with propranolol, will there be a greater hypoxemia in the CHD dogs? This study investigated the changes in the heartworm positive dog's submaximal exercise performance with respect to normal submaximal exercise and compared to control dogs.

Methods

All the dogs in experiment 1 were utilized in experiment 2. A random test order of the normal and beta-blocked exercise runs was assigned to each subject. The preparation for the exercise test was the same in both conditions, except for an i.v. injection of propranolol prior to the beta blocked exercise test. A 2 mg/kg dose of propranolol was dissolved in 20 cc of Lactated Ringer's and administered through a filter via the jugular catheter over a 10 min period. The protocol for the data collection, the treadmill test, and blood analyses were identical to those in experiment 1.

Sham Infusion Exercise

In addition to the normal and beta blocked exercise experiments, a sham infusion exercise study was performed on four dogs, two from each group. This was done to determine the influence of a 20 cc injection of Lactated Ringer's without propranolol. The procedures were the same as the beta blocked exercise procedures.

Statistical Analysis

Sham Infusion Exercise

ANOVA with a two (group) by two (condition) by eight (workload) factorial design was utilized to analyze arterial and venous pH, PCO_2, PO_2 and HCO_3^-, Hct, HR, MABP, Tr, Na^+, K^+, Cl^-, La, and Glu to determine if the infusion without propranolol affected the dogs. If there was a significant condition effect, a t-test between resting preinfusion and postinfusion data was made to ascertain if any changes occurred before exercise. An alpha level of .05 was set.

Beta Blocked Exercise

The design for all variables was completely random and a 2 (groups) x 2 (conditions) x 8 (workloads) factorial arrangement. Multivariate analysis of variance (MANOVA) was chosen to analyze the following data groupings:

1. Arterial blood gas and pH - pH, PCO_2, PO_2, and HCO_3^-
2. Venous blood gas and pH - pH, PCO_2, PO_2, and HCO_3^-
3. Electrolytes - Na^+, K^+, and Cl^-
4. Hct, HR, MABP, and Tr.

The Wilks'-Lambda Manova Test Criterion was consulted for overall group effect, condition effect, group by condition effect, workload effect, group by workload effect, condition by workload effect, and group by condition by workload effect. If a significant effect was found, the univariate ANOVA for the dependent variables was analyzed for the exact cause of difference. When ANOVA revealed a significant workload effect, a Newman-Keuls test was used to ascertain at which workload the variable differed. If a significant condition effect was found, a t-test on data

measured in four dogs before and after the infusion (prior to commencement of the exercise test) was performed to determine whether beta blockade affected that variable during rest. The La and Glu data were analyzed by univariate ANOVA, with a Newman-Keuls follow-up test for a significant workload effect and a t-test on pre- and post-infusion data for a significant condition effect. In the Glu analysis, only data from four dogs (2 in each group) were analyzed. Least square means at each workload were graphed when a significant group by workload, condition by workload, or group by condition by workload interaction was found. The alpha level selected was .05.

Paired t-tests between data at rest and at w 1, as well as between rest and w 7 data were done to reveal any differences heartworm infected dogs might have in their response to the beginning of exercise, or to the highest level of stress, when compared to resting data. In accordance with Bonferroni procedures, an alpha level of .025 was established for significance (alpha=.05/2).

Results

Sham Infusion Exercise

The submaximal exercise test produced the same responses across workloads in the sham experiment as during normal exercise in arterial and venous blood gases and pH, Hct, HR, MABP, T_r, and K^+. The condition effect was significant only in T_r ($F_{1,2}$=24.97; p=.0378) and K^+ ($F_{1,2}$=46.97; p=.0206). The t-test on T_r before and after the saline infusion was significant (p=.0325), with the preinfusion T_r being .17 ° C greater than post infusion T_r (39.3±.2° C vs 39.1±.2° C). There was a mean T_r of 39.6° C during the normal exercise experiment, while it was

39.2° C during the sham exercise experiment. The K^+ t-test for pre- and post-infusion levels did not show a significant change. The mean K^+ was greater during the sham run (5.13 mEq/L) than during the normal run (5.03 mEq/L). Detailed statistical tables are in Appendix D.

Beta Blocked Exercise

ANOVA with a 2 x 2 x 8 factorial design was used to analyze La and Glu. MANOVA with a 2 x 2 x 8 factorial design was applied to arterial and venous blood gas (pH, PCO_2, PO_2, and HCO_3^-), Hct, HR, MABP, Tr, Na^+, K^+, and Cl^-. Tables 8, 9, and 10 summarize the significant effects and interactions of the variables. The significant paired t-tests are noted in Table 11. All detailed MANOVA and ANOVA tables are presented in Appendix E.

Table 8

Summary of Significant Effects and Interactions for Beta Block vs Normal Conditions

Description	ANOVA
Lactate	
Group	
Condition	
Group x Condition	
Workload	*
Group x Workload	
Condition x Workload	
Group x Condition x Workload	
Glucose	
Group	
Condition	*
Group x Condition	
Workload	
Group x Workload	
Condition x Workload	
Group x Condition x Workload	

* = $p<.05$

Table 9

Summary of Significant Effects and Interactions for Beta Block vs Normal Conditions

Description	MANOVA	ANOVA			
Electrolytes		Na^+	K^+	Cl^-	
Group	*	**			
Condition	**		**		
Group x Condition					
Workload	**		**	**	
Group x Workload	*	*		**	
Condition x Workload	*		*		
Group x Condition x Workload			*		
Other Physiological Parameters		Hct	HR	MABP	Tr
Group					
Condition			**		
Group x Condition					
Workload	**	**	**	**	**
Group x Workload	**	*		**	
Condition x Workload	**		**	*	
Group x Condition x Workload					**

* = $p<.05$
** = $p<.01$

Table 10

Summary of Significant Effects and Interactions for Beta Block vs Normal Conditions

Description	MANOVA	ANOVA			
Arterial Blood Gas and pH		pH	PCO_2	PO_2	HCO_3^-
Group	*			**	
Condition				*	
Group x Condition				*	
Workload	**	**	**		**
Group x Workload	**			**	
Condition x Workload					
Group x Condition x Workload					
Venous Blood Gas and pH		pH	PCO_2	PO_2	HCO_3^-
Group					
Condition	*	**		*	
Group x Condition					
Workload	**		*	*	
Group x Workload			*		
Condition x Workload	*				
Group x Condition x Workload					

* = $p < .05$
** = $p < .01$

Table 11

Summary of Significant Paired t-Tests for the Beta Block Condition

	Heartworm Dogs		Control Dogs	
Comparison:	Rest-w 1	Rest-w 7	Rest-w 1	Rest-w 7
PARAMETER				
Arterial Blood				
pH	*			
PCO_2				
PO_2			*	*
HCO_3^-				
Venous Blood				
pH				
PCO_2		*		*
PO_2	*			*
HCO_3^-				
Hematocrit				
Heart Rate	*	*	*	*
Mean Blood Pressure	*	*		
Rectal Temperature		*		
Sodium				
Potassium	*	*	*	*
Chloride				
Lactate				
Glucose				

* = significant at $-t_{\alpha/2} < p$ or $p > +t_{\alpha/2}$
alpha = .025

Lactate

Lactate analysis by ANOVA revealed only a significant workload effect ($F_{7,84}$=2.5; p=.0221). However, a Newman-Keuls follow-up failed to disclose any differences between the means across exercise (Figure 13). There were no significant paired t-tests for the onset of work and the highest level of work during exercise after beta blockade (Tables E-24 & E-25). No significant group, group by condition, workload, group by workload, condition by workload, or group by condition by workload effects were revealed (Table E-22).

Glucose

Submaximal exercise produced a significant condition effect on Glu levels ($F_{1,2}$=19.12; p=.0485). The mean Glu during beta blockade (106.7 ±4.3 mg/dl) was greater than the mean Glu without propranolol (89.7±1.4 mg/dl). A t-test comparing Glu levels before (87.6±3.3 mg/dl) and after (109.4±2.5 mg/dl) the infusion of propranolol prior to exercise disclosed that the propranolol significantly increased the Glu levels at rest (t_3=3.47; p=.98). Changes at the beginning of exercise and at w 7 compared to rest were not significant (Tables E-24 & E-25). There were no significant group, group by condition, workload, group by workload, condition by workload, or group by condition by workload effects for Glu (Table E-23).

Electrolytes

MANOVA and the Wilks-Lambda Criterion revealed significant differences in the overall group effect ($F_{3,4}$=9.61; p=.0267), the overall condition effect ($F_{3,4}$=132.78; p=.0002), the overall workload effect ($F_{21,236}$=8.51; p=.0001), the overall group by workload effect

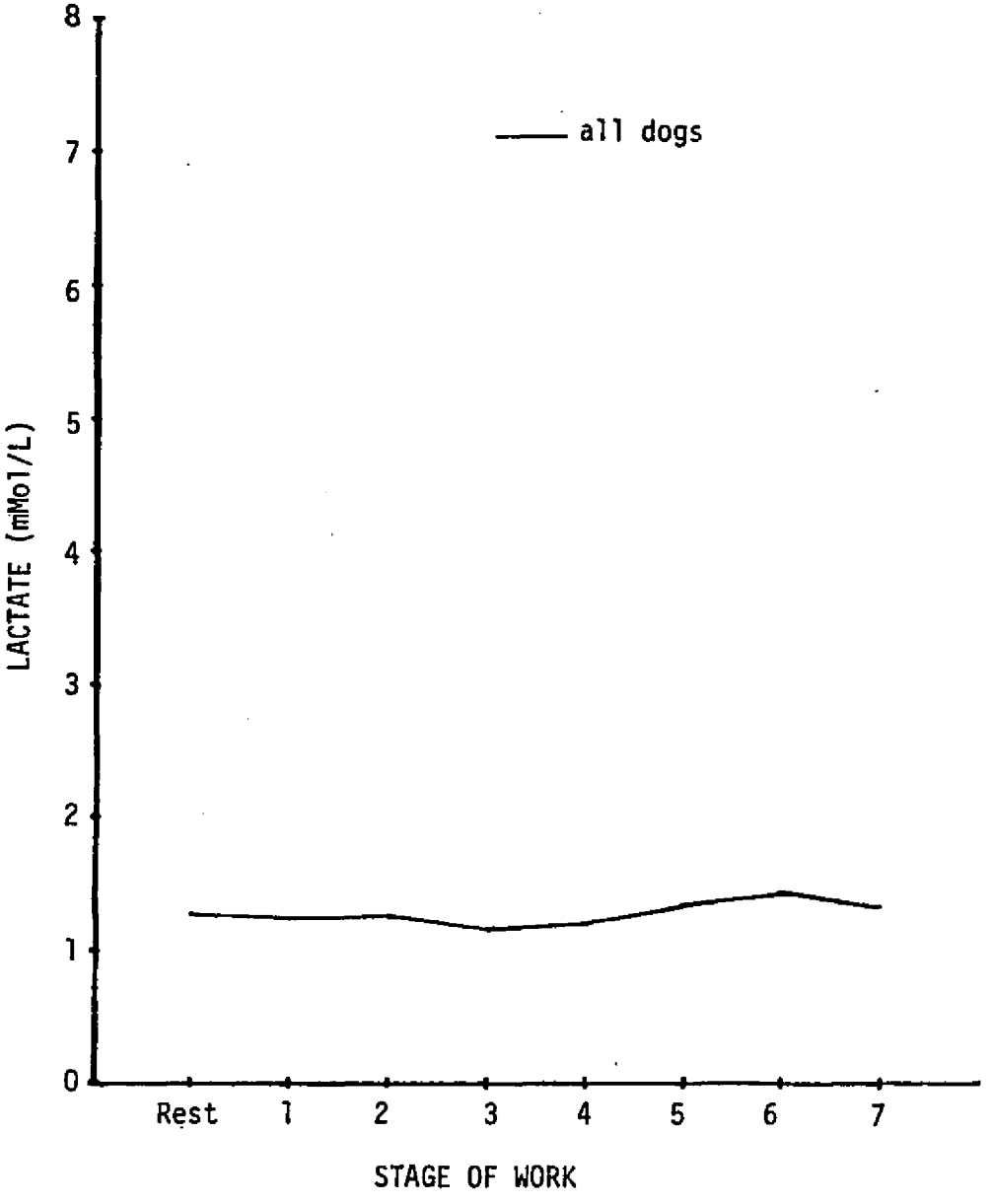

Figure 13. Beta Block vs Normal Exercise: Means of Lactate

($F_{21,236}$=1.74; p=.0256), and the overall condition by workload effect ($F_{21,236}$=1.77; p=.0221). Neither the overall group by condition effect nor the overall group by condition by workload effect were significant (Table E-18).

Sodium

Through ANOVA, the significant group difference was attributed to Na^+. The group Na^+ mean for the CHD dogs (142.9±.45 mEq/L) was less than the N dogs (146.2±.74 mEq/L). There was also a significant group by workload effect on Na^+ ($F_{7,84}$=2.19; p=.043). Not only were the CHD dogs' Na^+ significantly lower at rest and during each workload, their exercise values did not differ from the resting value. The N dogs had a significant increase above resting Na^+ during w 4 through w 6 (Figure 14). The comparisons between resting data and those at w 1 and w 7 revealed no significant changes (Tables E-24 & E-25). There were no condition, group by condition, workload, condition by workload, or group by condition by workload significant effects for Na^+ (Table E-19).

Potassium

The ANOVA for K^+ did not demonstrate any significant group, group by condition, or group by workload effects following beta blockade (Table E-20). There was a significant condition effect seen in K^+ ($F_{1,6}$=77.2; p=.0001). During beta blockade, the mean K^+ (5.42±.24 mEq/L) was significantly greater than the mean K^+ during normal conditions (5.0±.15 mEq/L). In four of the dogs, a comparison of K^+ before (4.6 ±.06 mEq/L) and after (4.84 ±.15 mEq/L) the propranolol infusion was made. The t-test revealed a significant increment during rest (t_3=3.87; p=.985). There was a significant workload effect ($F_{7,84}$=38.39; p=.0001). Exercise produced significantly greater K^+

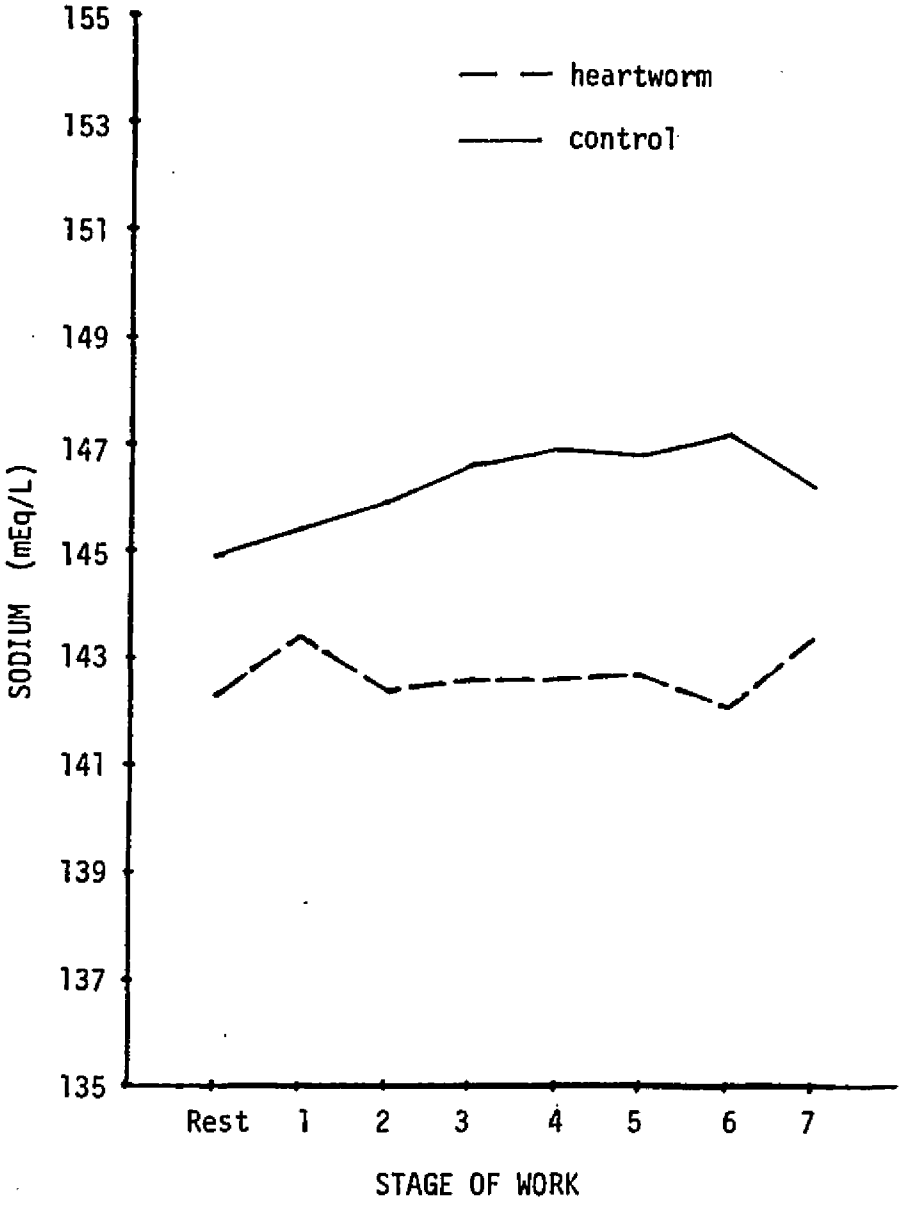

Figure 14. Beta Block vs Normal Exercise: Group Means of Sodium

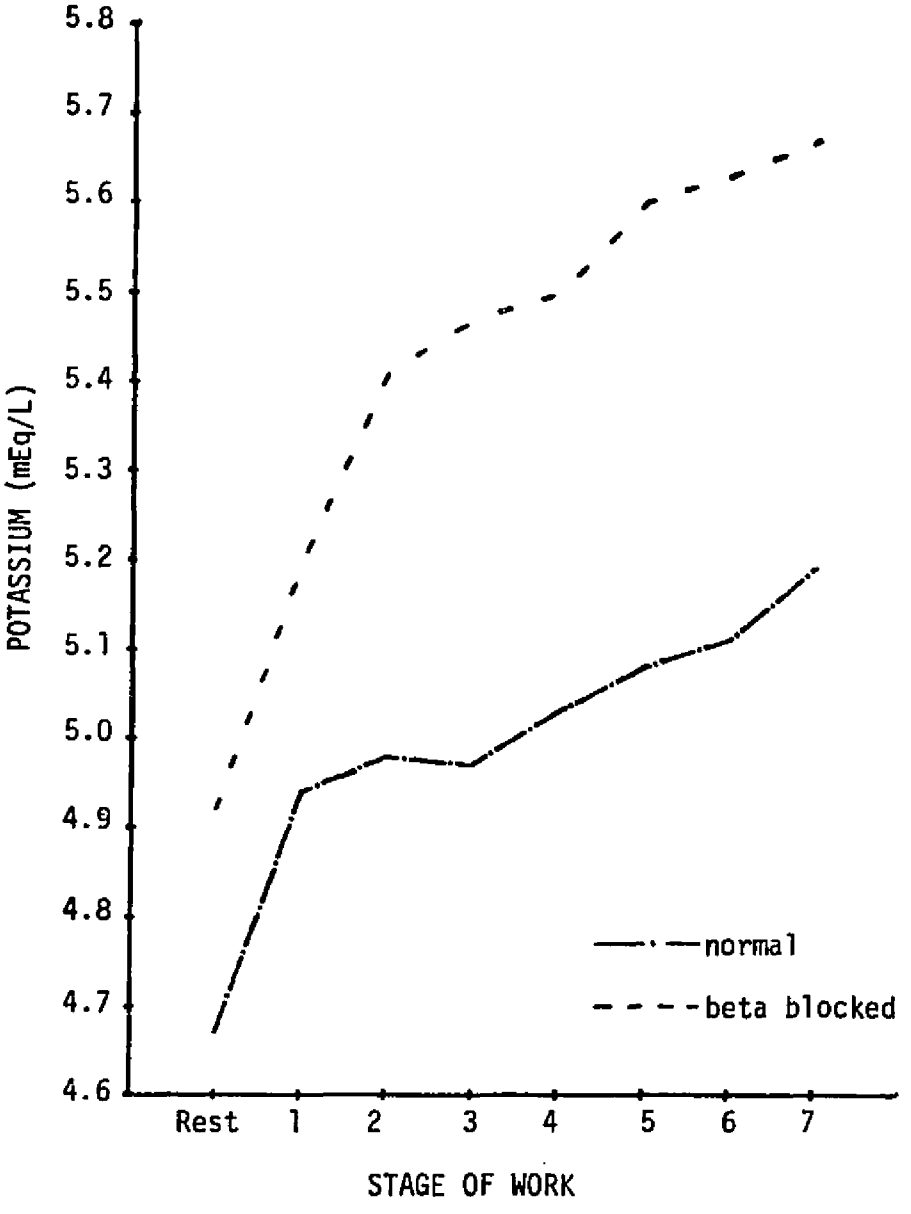

Figure 15. Beta Block vs Normal Exercise: Condition Means of Potassium

levels than those at rest. The Newman-Keuls also revealed another significant increase at w 2. The next significant K^+ increment greater than w 2's level occurred at w 5. In addition to changes observed in exercise, beta blockade produced a significant condition by workload effect ($F_{7,84}$=2.8; p=.0115) in K^+ (Figure 15). During both beta blocked exercise and normal exercise, the resting K^+ was significantly lower than their respective exercise K^+ values. During both types of exercise, there were no significant variations in K^+, but all beta blocked K^+ were significantly greater than the normal exercise K^+ levels.

Although MANOVA did not reveal a significant overall group by condition by workload effect for the electrolytes, the K^+ ANOVA did show that interaction to be significant ($F_{7,84}$=2.84; p=.0105). During beta blocked exercise, the K^+ increased significantly above rest at w 2 in the CHD group and at w 3 in the N dogs. Those significant increments were one workload later for CHD dogs and one workload earlier for N dogs than noted during normal exercise. However, a paired t-test for the transition to exercise (CHD: t_3=3.81; p=.989; N: t_3=8.66; p=.998) and for the greatest w (CHD: t_3=4.33; p=.99; N: t_3=5.09; p=.993) revealed both increments above resting levels were significant in both groups. At the highest level of stress following propranolol, the CHD dogs' K^+ was greater than N dogs at w 7, as well as greater than both groups' w 7 K^+ during normal exercise (Figure 16). With the exception of w 7 in beta blocked exercise, the CHD had consistently, but insignificantly, greater K^+ levels than the N dogs during beta blocked exercise, as had been reported during normal exercise.

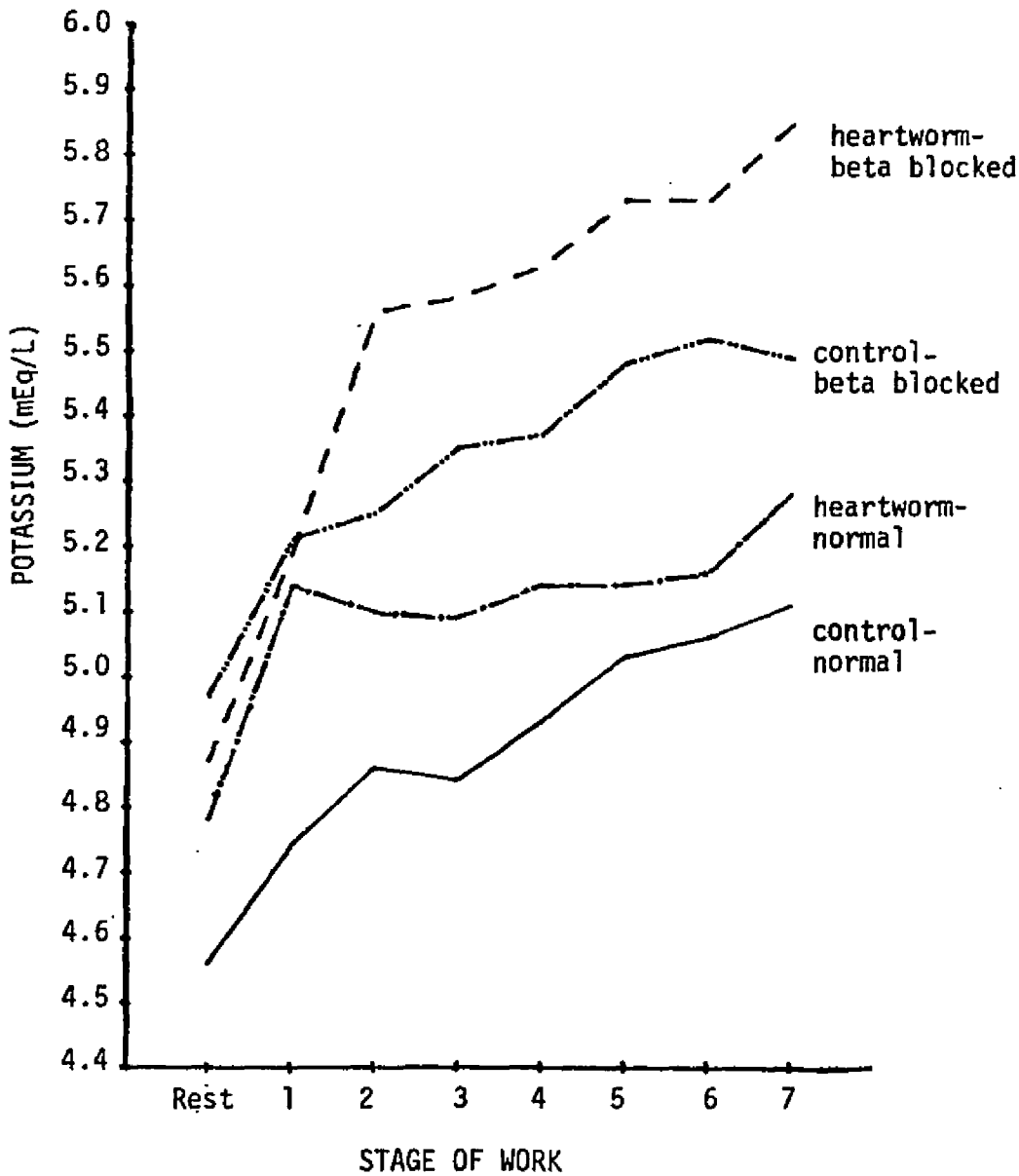

Figure 16. Beta Block vs Normal Exercise: Group x Condition Means of Potassium

Figure 17. Beta Block vs Normal Exercise: Group Means of Chloride

Chloride

Submaximal treadmill exercise produced a significant workload effect ($F_{7,84}$=4.07; p=.0007). The Newman-Keuls analysis showed that resting Cl^- was less than only that at w 6 and w 7. A significant group by workload effect ($F_{7,84}$=3.14; p=.0053) in Cl^- was also found. During exercise, the CHD dogs' Cl^- was similar to resting levels. Their w 2 and w 3 levels were lower than their w 7 level. The N dogs' Cl^- increased significantly above resting levels at w 4, and again at w 6 through w 7. All the N dogs' exercise Cl^- levels were similar. At each workload, from w 2 through w 6, the CHD dogs had significantly lower Cl^- than the N dogs at the same workload (Figure 17). The paired t-tests did not display significant changes from rest to w 1 or from rest to w 7 (Tables E-24 & E-25). No significant differences were shown in group, condition, group by condition, condition by workload, or group by condition by workload effects (Table E-21).

Other Physiological Parameters

The MANOVA and Wilks-Lambda Criterion for Hct, HR, MABP, and Tr demonstrated significant overall workload ($F_{28,242}$=15.98; p=.0001), group by workload ($F_{28,243}$=1.93; p=.0046), and condition by workload ($F_{28,243}$=3.62; p=.0001) effects. There were no significant group, condition, group by condition, or group by condition by workload effects (Table E-11).

Hematocrit

The ANOVA for Hct did not show any significant differences in the group, condition, group by condition, condition by workload, or group by condition by workload effects (Table E-12). However, there were

significant workload ($F_{7,70}$=31.73; p=.0001) and group by workload ($F_{7,70}$=2.47; p=.0250) differences. Without distinguishing between groups, exercise produced a significantly higher Hct with the onset of exercise. The response across exercise was fairly linear, with significant changes appearing about 3 workloads apart. However, there were some differences between the group responses to exercise (Figure 18). The increments in N dogs' Hct were not significant changes. Commencing with w 2, the CHD dogs' Hct was significantly greater than their resting Hct. Both groups had similar exercise Hct values. The paired t-tests for each groups' response in the transition to exercise and at the highest level of exercise compared to rest were not significant (Table E-24 & E-25).

Rectal Temperature

Submaximal exercise stimulated significant changes in T_r ($F_{7,70}$=35.17; p=.0001). However, there were no significant group, condition, group by condition, group by workload, or condition by workload effects displayed (Table E-15). Figure 19 represents the mean T_r responses to each workload in all the exercise tests. As revealed by the Newman-Keuls test, the first significant change above resting T_r appeared at w 3, after which significant changes occur every two workloads (1<3, 2<4, and 3<5) until w 4. The T_r at w 4, w 5, and w 6 are significantly different.

Contrary to the nonsignificant group by condition by workload effect reported in the MANOVA, the interaction was significant in the ANOVA for T_r ($F_{7,70}$=4.61; p=.0003). The paired t-test for the transition to exercise was not significant for either group during beta blocked exercise (Tables E-24 & E-25), just as reported for normal

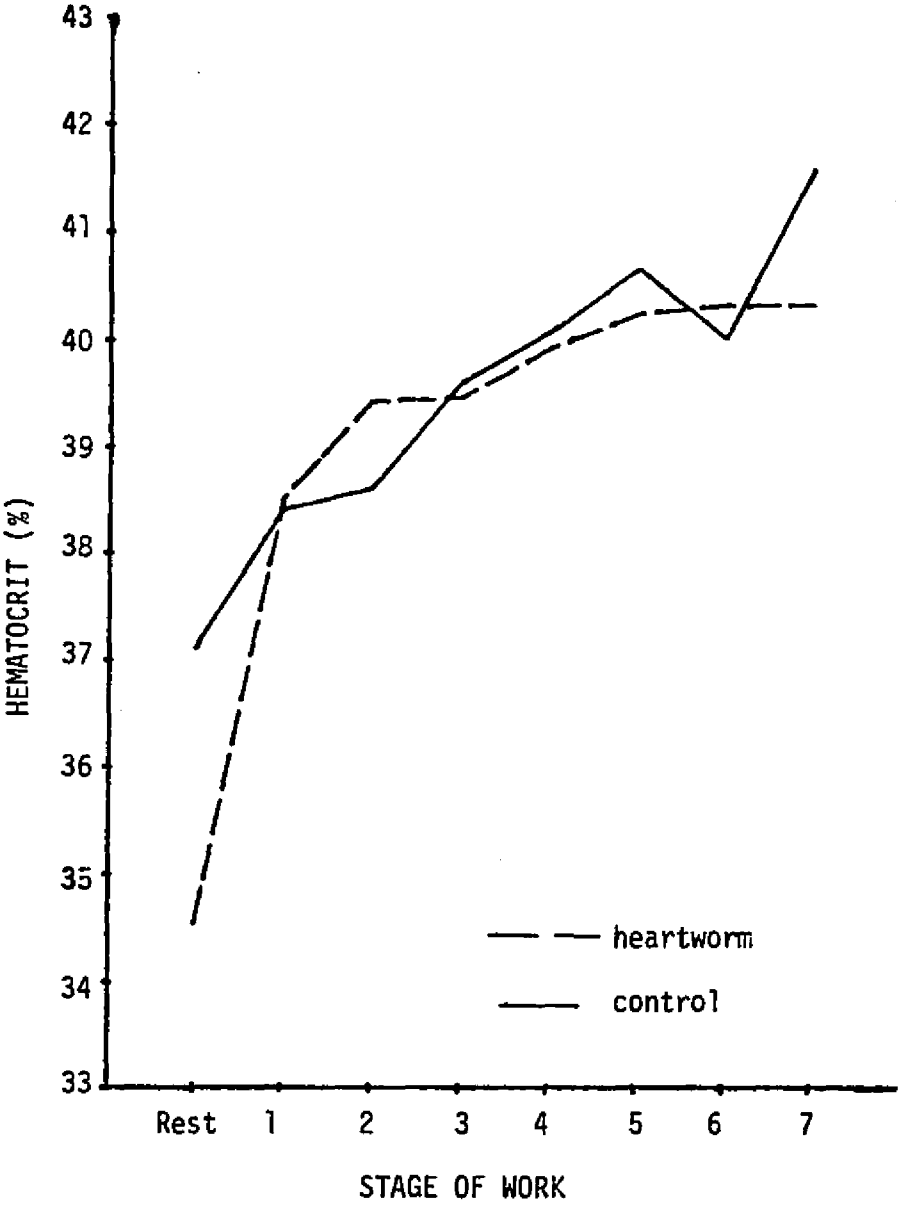

Figure 18. Beta Block vs Normal Exercise: Group Means of Hematocrit

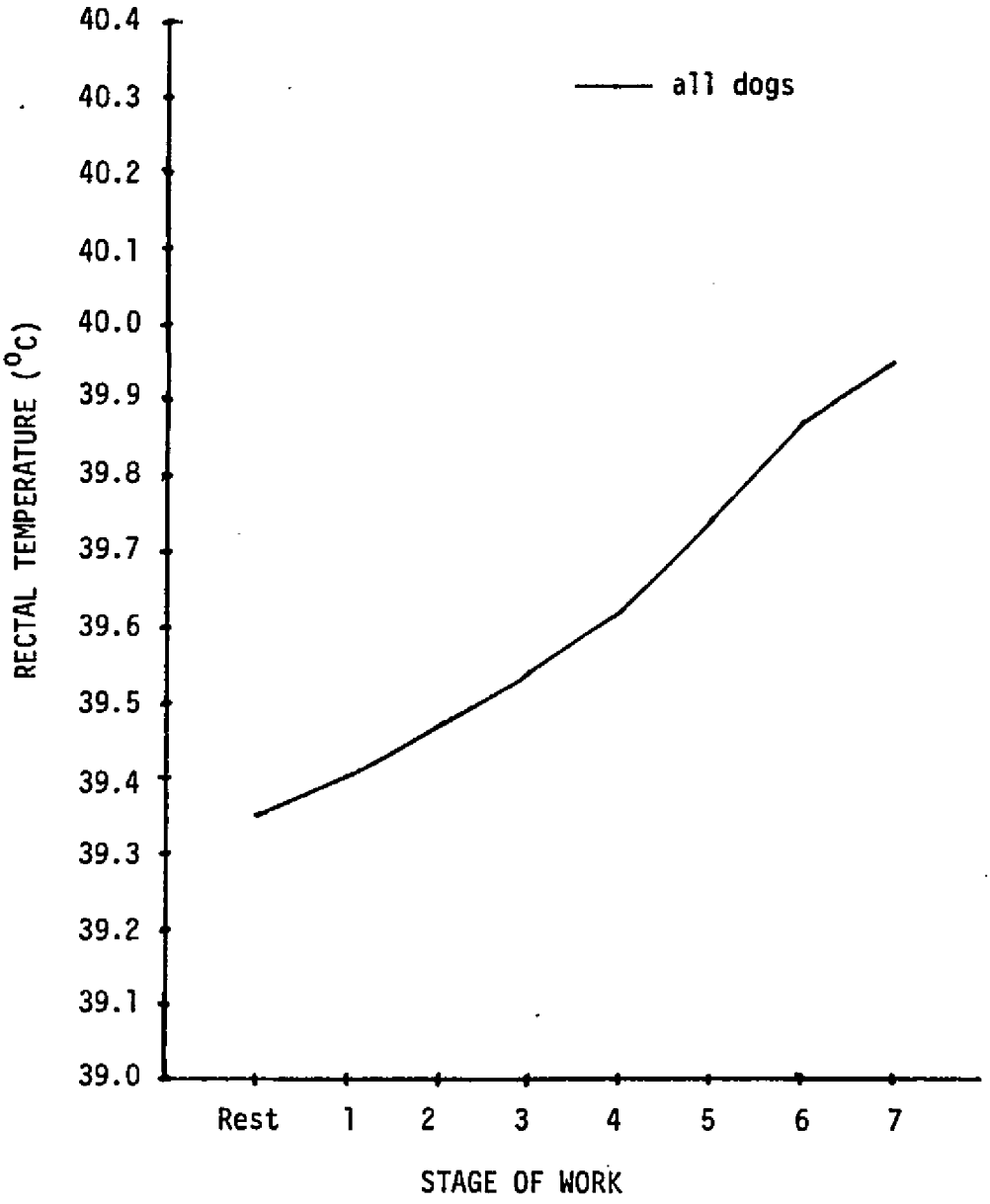

Figure 19. Beta Block vs Normal Exercise: Means of Rectal Temperature

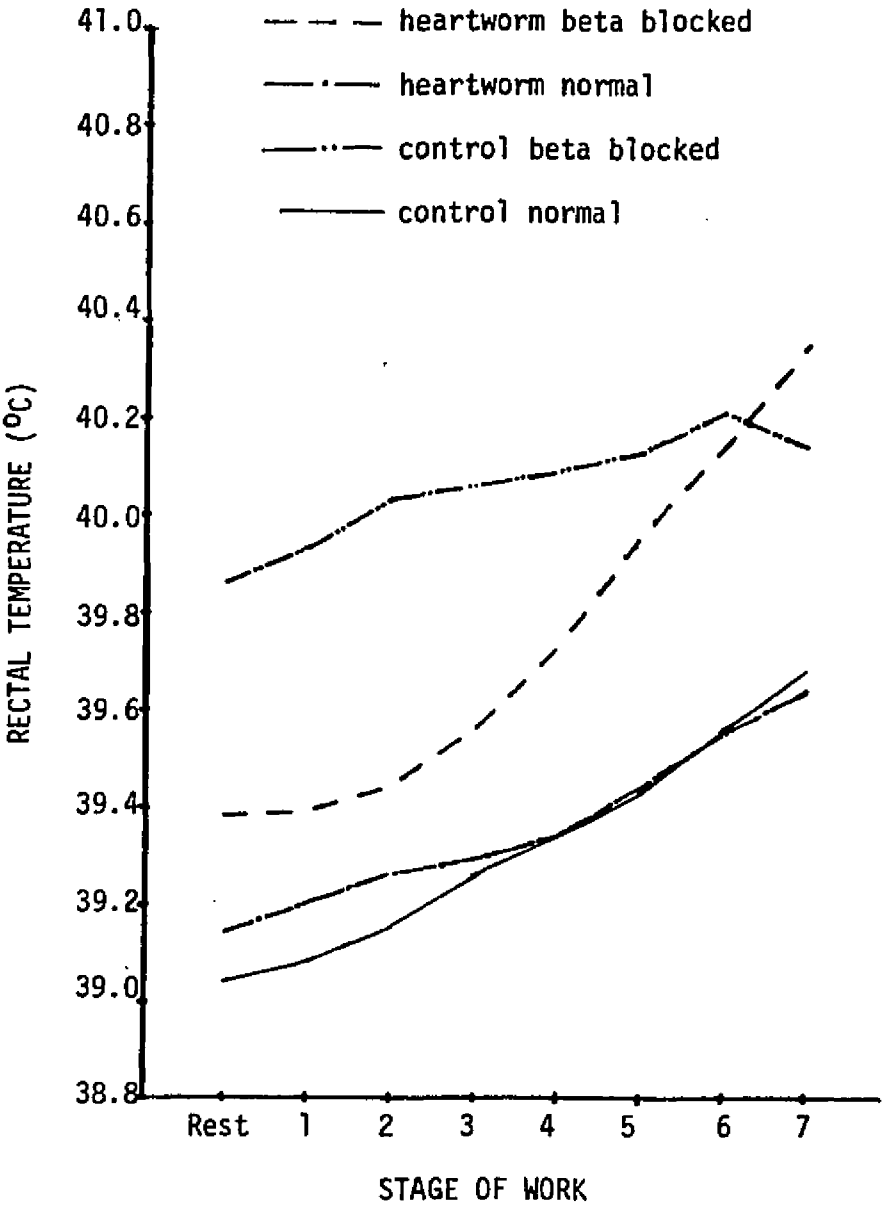

Figure 20. Beta Block vs Normal Exercise: Group x Condition Means of Rectal Temperature

exercise. The comparison from rest to w 7 was not significant for the N dogs (Tables E-24 & E-25), while it had been in normal exercise. The opposite results were found for the CHD dogs in beta blocked exercise. The increase above resting T_r at w 7 was significant ($\underline{t}_3$=4.59; p=.99) in beta blocked exercise, but not in normal exercise. From rest through w 7, there were no significant changes in T_r during normal exercise for the CHD dogs or the N dogs, and during beta blocked exercise for the N dogs (Figure 20). However, the beta blocked CHD dogs did show a significant change in T_r at w 7. The T_r in the final workload was greater than their resting, w 1 and w 2 T_rs during that test. In addition, it was greater than values for T_r at rest through w 5 in both groups' normal exercise tests. The N dogs' w 7 T_r during beta blockade was greater than the T_r at rest through w 3 during normal exercise for both groups.

Heart Rate

The group HR means were not significantly different, but the mean HR for beta blockade (146.8±18.2 bpm) was significantly less than the mean HR for normal conditions (196.4±37 bpm) ($\underline{F}_{1,2}$=19.52; p=.0069). At rest, propranolol did not significantly change the HR, as revealed by a comparison of pre- and post-infusion HR in four dogs. Exercise did produce some significant HR differences ($\underline{F}_{7,70}$=100.72; p=.0001), which were muted by beta blockade (Figure 21). The condition by workload effect was significant ($\underline{F}_{7,70}$=13.58; p=.0001). The onset of exercise produced a significant increase in HR in both normal and beta blocked exercise. As normal exercise produced significant increases from resting HR to w 1 and from resting HR to w 7, the same significance was noted in beta blocked exercise (Tables E-24 & E-25). Exercise following

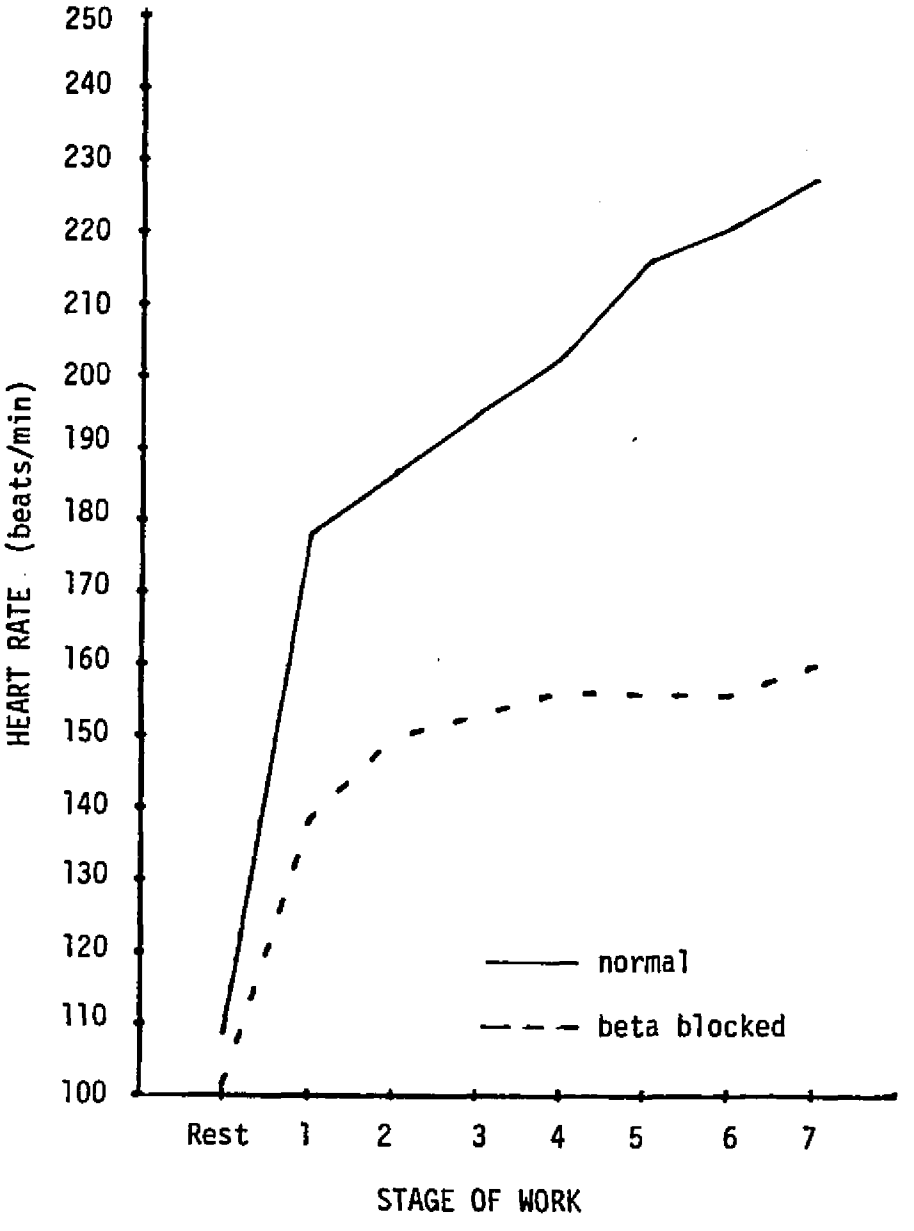

Figure 21. Beta Block vs Normal Exercise: Condition Means of Heart Rate

propranolol produced a significant increment in both groups in the transition to exercise (CHD: $\underline{t}_3$=21.72; p=.9999; N: $\underline{t}_3$=5.67; p=.995) and from rest to w 7 (CHD: $\underline{t}_3$=8.95; p=.9986; N: $\underline{t}_3$=5.35; p=.994). After w 1, there were no further HR changes observed during exercise following administration of propranolol, unlike during normal exercise. In exercise without propranolol, HR at w 5 was greater than those in the first three workloads, and HR at w 6 and w 7 were greater than the first four w HR. At each workload, propranolol produced a significantly lower HR than seen at each workload in normal exercise. There were no other significant effects for HR (Table E-13).

Mean Arterial Blood Pressure

ANOVA revealed no significant differences in the group, condition, group by condition, or group by condition by workload effects for MABP (Table E-14). Exercise produced significant changes in MABP ($\underline{F}_{7,70}$=10.48; p=.0001). The Newman-Keuls test showed all exercise MABP were greater than the resting MABP. There were differences noted between the groups' MABP response to exercise ($\underline{F}_{7,70}$=3.32; p=.0041). These group responses are the average of both normal exercise and beta blocked exercise at each workload (Figure 22). The N dogs did not have any significant changes, where the CHD dogs had a significant increase in MABP with w 1. This was maintained across exercise. There were no differences between the N dogs' exercise MABP values and the CHD dogs' exercise MABP values.

Beta blockade produced significant differences in the condition by workload effect ($\underline{F}_{7,70}$=2.88; p=.0106). During normal exercise, the MABP increased significantly with the onset of exercise and remained elevated throughout the test. All exercise MABP values were similar. During beta

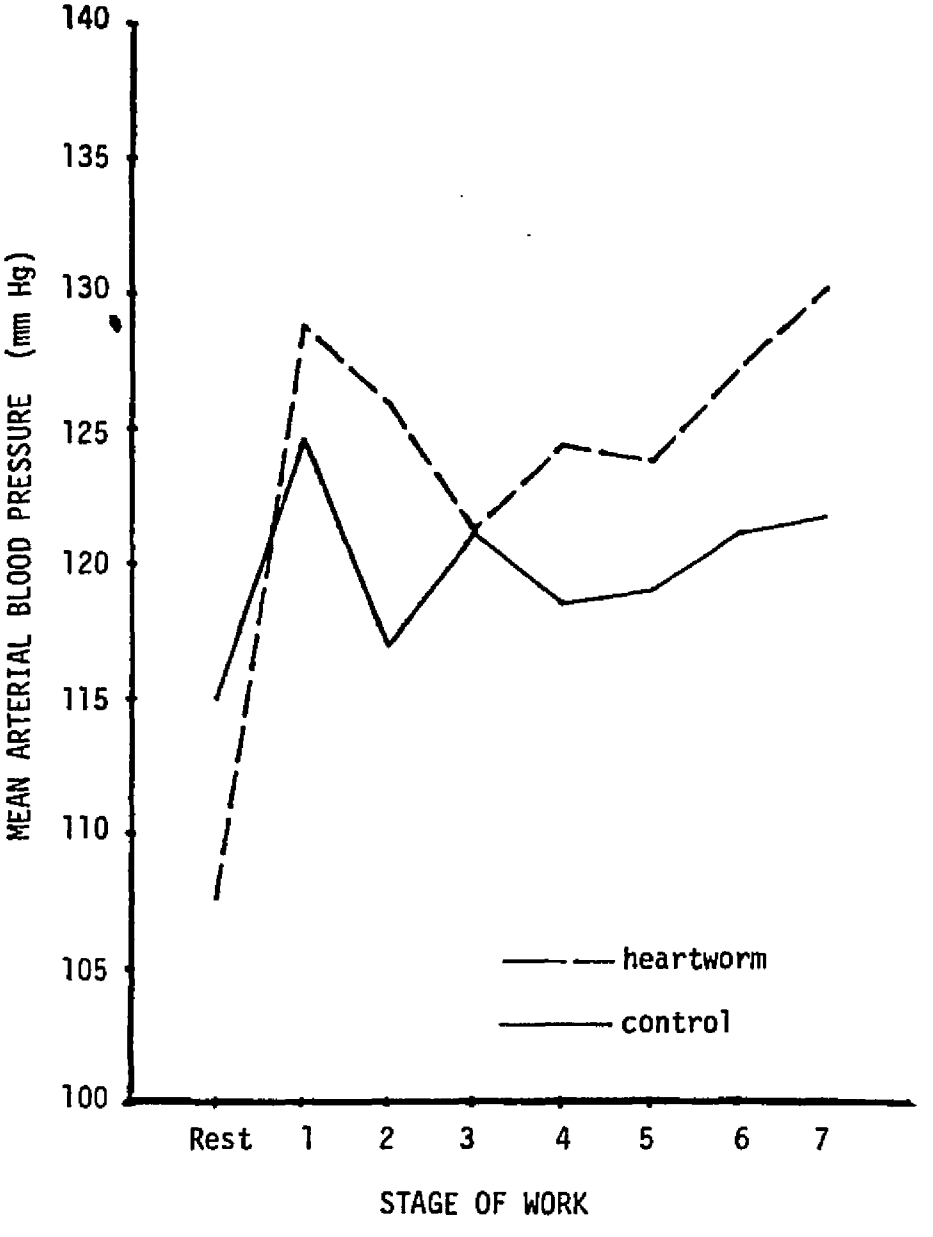

Figure 22. Beta Block vs Normal Exercise: Group Means of Mean Arterial Blood Pressure

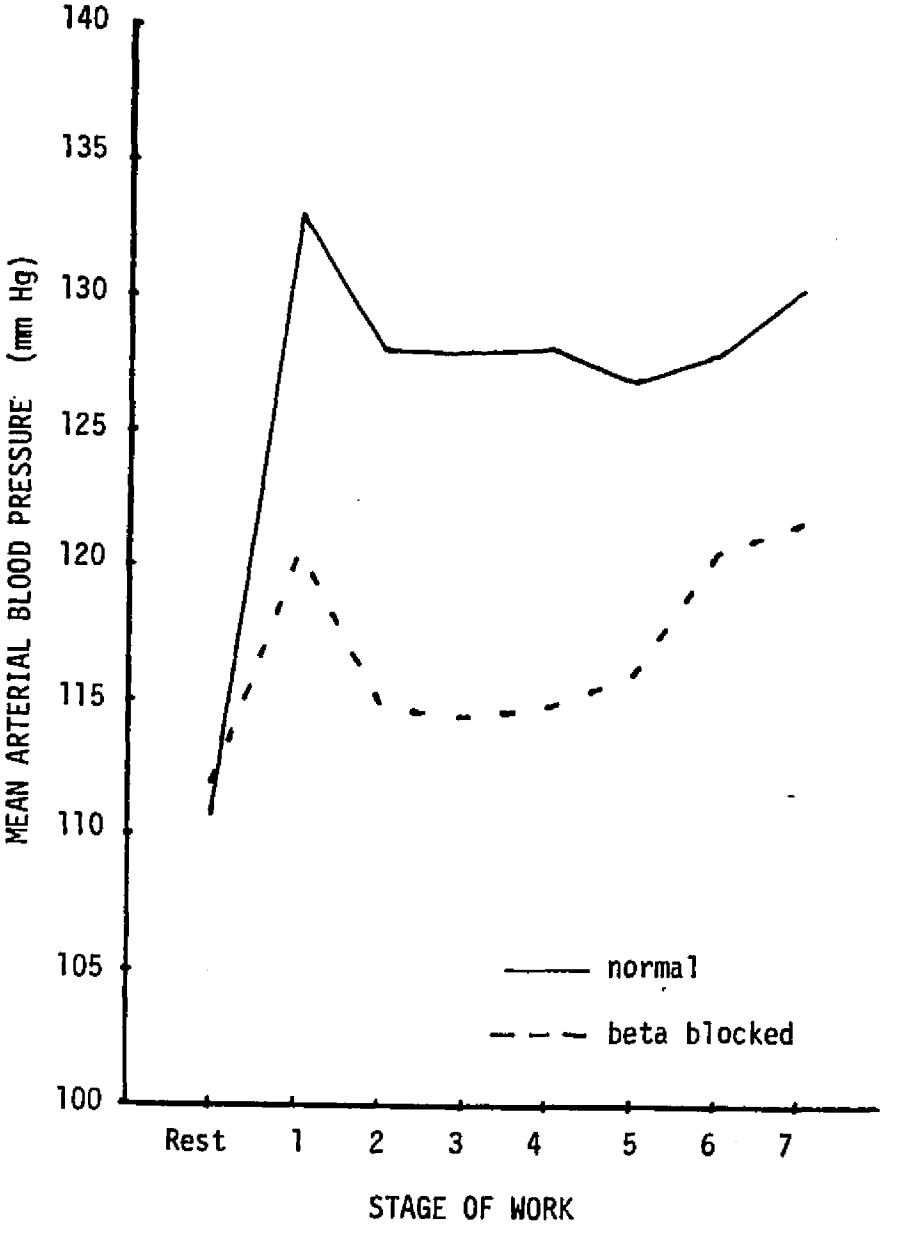

Figure 23. Beta Block vs Normal Exercise: Condition Means of Mean Arterial Blood Pressure

blocked exercise, there were no significant changes in MABP from resting MABP (Figure 23). The paired t-tests for beta blocked exercise at the onset of exercise and at the highest workload were not significant for the N dogs (Tables E-24 & E-25). The CHD dogs had significant paired t-tests in beta blocked exercise when resting MABP was compared to that at w 1 (t_3=5.18; p=.993) and to that at w 7 (t_3=5.36; p=.994).

Arterial Blood Gas and pH

The MANOVA and Wilks-Lambda Criterion disclosed significant overall group ($F_{4,3}$=11.9; p=.0348) and workload ($F_{28,293}$=2.75; p=.0001) effects in the arterial blood gas and pH. Additionally, there was a significant overall group by workload effect ($F_{28,293}$=2.75; p=.001) for these variables. No significant overall condition, group by condition, condition by workload, or group by condition by workload effects were found in the arterial blood gas and pH MANOVA (Table E-1).

Arterial pH

ANOVA for arterial pH did not reveal any significant differences for the group, condition, group by condition, group by workload, condition by workload, or group by condition by workload effects (Table E-2). There was a significant workload effect ($F_{7,84}$=6.88; p=.0001). The resting arterial pH was significantly lower than all exercise values of arterial pH (Figure 24). There were no further significant changes. The paired t-test for beta blocked exercise was significant in the CHD dogs transition to exercise (t_3=6.14; p=.996), but not in the N dogs. Neither group had a significant gain from rest at the highest workload (Tables E-24 & E-25).

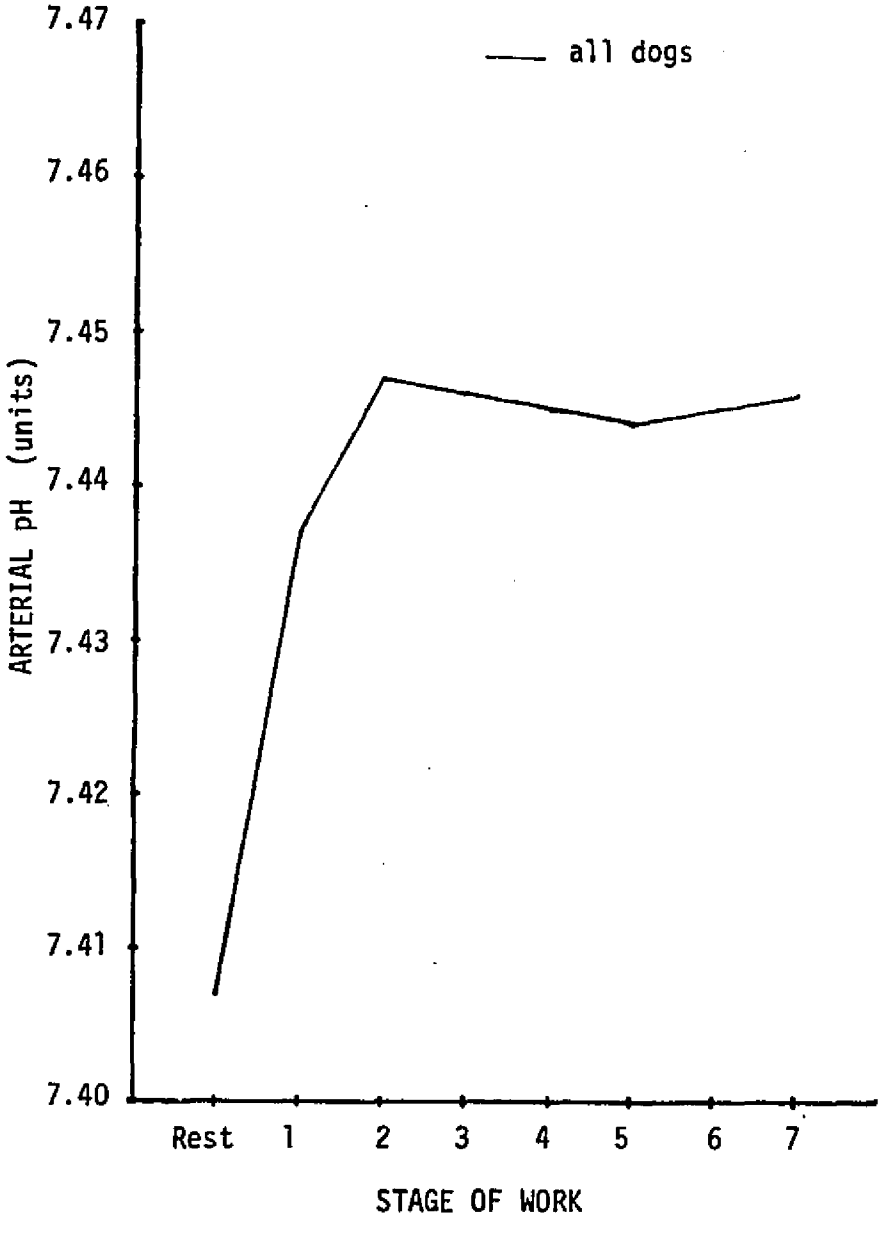

Figure 24. Beta Block vs Normal Exercise: Means of Arterial pH

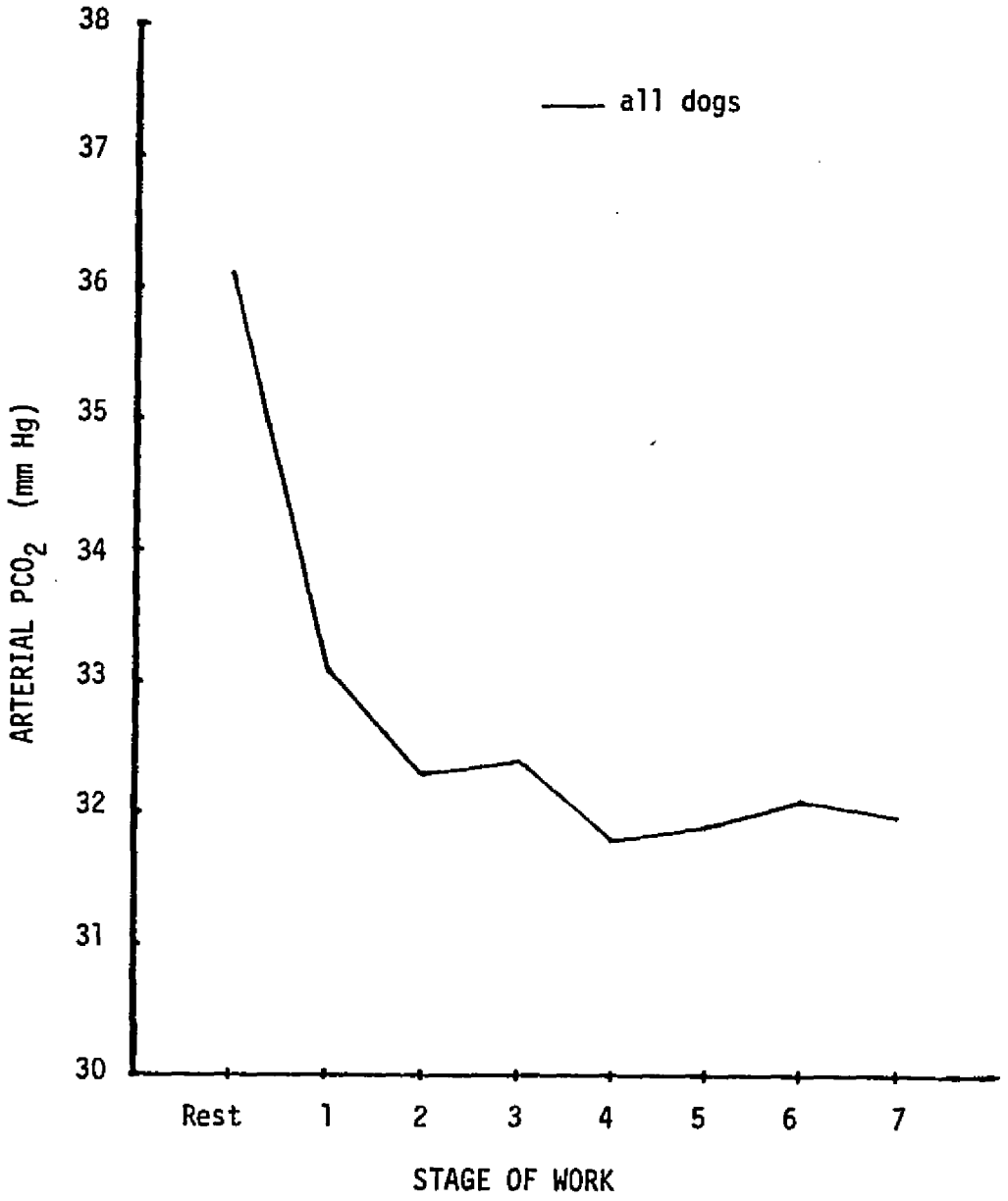

Figure 25. Beta Block vs Normal Exercise: Means of Arterial PCO_2

Arterial PCO_2

No group, condition, group by condition, group by workload, condition by workload, or group by condition by workload differences were found in P_aCO_2 (Table E-3). Exercise did cause significant differences in P_aCO_2 ($F_{7,84}$=7.24; p=.0001). At the beginning of exercise, there was a significant drop below resting P_aCO_2 which persisted throughout exercise (Figure 25). The exercise P_aCO_2 values did not differ. The paired t-tests comparing rest and w 1 and rest and w 7 after propranolol were not significant in either group (Tables E-24 & E-25).

Arterial PO_2

The CHD dogs' mean P_aO_2 (89.1±2.1 mm Hg) was significantly lower than that of the N dogs (106.4±3.4) ($F_{1,6}$=17.68; p=.0057). During beta blockade, the mean P_aO_2 (100.1±2.4 mm Hg) was greater than that during normal conditions (95.3±1 mm Hg) ($F_{1,6}$=7.86; p=.031). A comparison between pre- and post-infusion P_aO_2 was not significant. The propranolol injection did not affect the resting P_aO_2 levels in four dogs significantly. There were significant group by condition effects observed ($F_{1,6}$=6.31; p=.0458). The N dogs had similar P_aO_2 means during normal conditions (106.1±2.3 mm Hg) and beta blocked conditions (106.6±5 mm Hg). During beta blockade, the CHD dogs had significantly greater P_aO_2 (93.6±1.5 mm Hg) than without propranolol (84.5±3 mm Hg).

Exercise did not produce significant changes in P_aO_2. There were no significant condition by workload or group by condition by workload effects (Table E-4). However, there was a significant group by workload effect found ($F_{7,84}$=5.23; p=.0001). Neither group had significant changes from their resting P_aO_2, but all N dogs' exercise

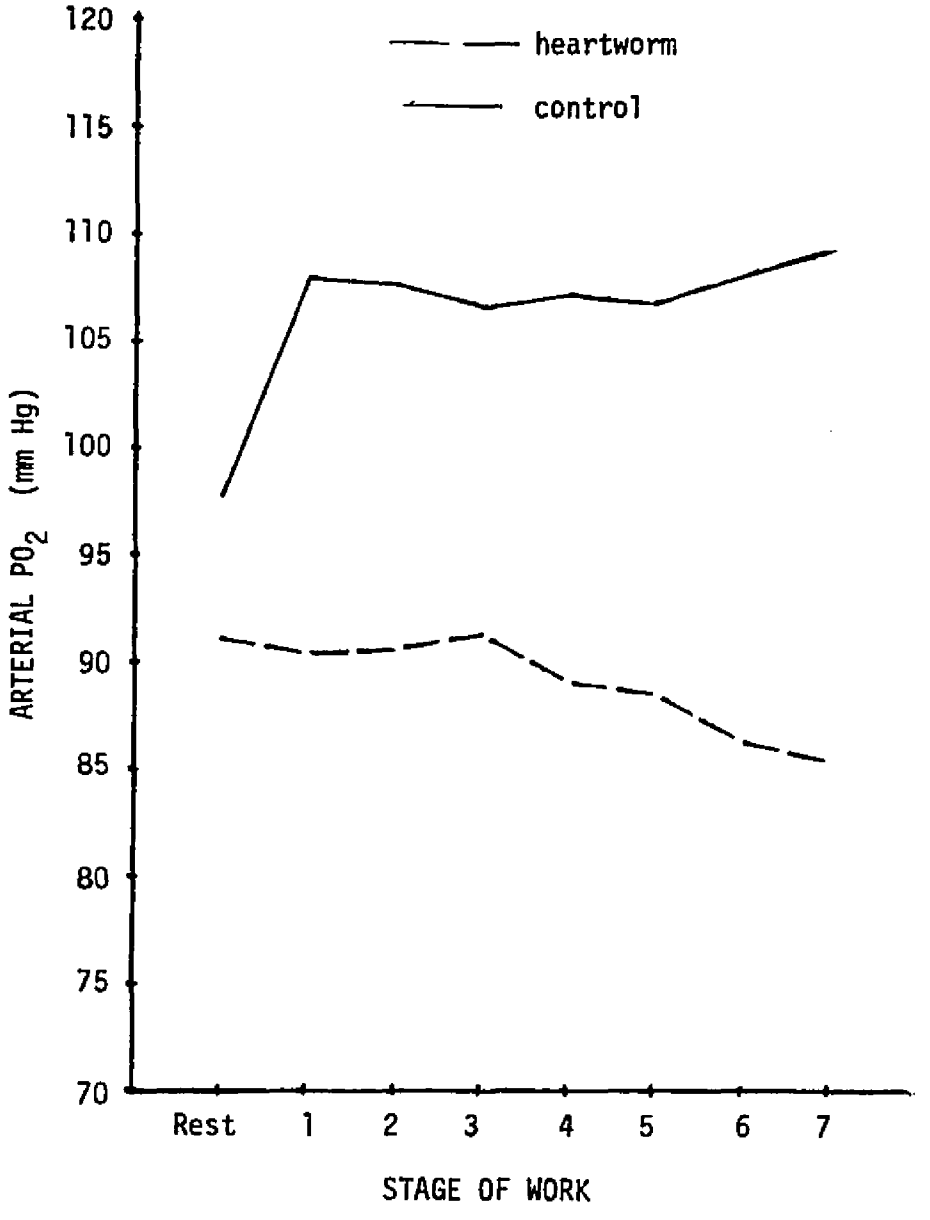

Figure 26. Beta Block vs Normal Exercise: Group Means of Arterial PO_2

P_aO_2 were greater than all exercise P_aO_2 values in the CHD dogs. The two groups' resting values were similar; however, the N dogs' resting P_aO_2 was greater than the CHD dogs' values from w 4 through w 7 (Figure 26). The paired t-tests for rest and the onset of exercise and for rest and the highest level of work were not significant for the CHD dogs (Tables E-24 & E-25), but were for the N dogs. At w 1, the N dogs had a significant increment above resting P_aO_2 (t_3=5.76; p=.995). That increment was maintained throughout exercise. Therefore, when compared to changes from rest, the P_aO_2 at w 7 was also significant (t_3=8.19; p=.998).

Arterial HCO_3^-

The arterial HCO_3^- ANOVA revealed a significant workload effect ($F_{7,84}$=2.96; p=.008). The Newman-Keuls revealed a significant drop in arterial HCO_3^- from resting levels at w 4. Resting arterial HCO_3^- was greater than those at w 4 through w 7 (Figure 27). All exercise values were similar. The comparisons between rest and w 1 and between rest and w 7 were not significant for either group (Tables E-24 & E-25). There were no significant group, condition, group by condition, condition by workload, or group by condition by workload effects for arterial HCO_3^- (Table E-5).

Venous Blood Gas and pH

In the venous blood gas variables, no overall group, group by condition, group by workload, or group by condition by workload differences were revealed (Table E-6). MANOVA and the Wilks-Lambda Criterion showed overall condition ($F_{4,3}$=17.69; p=.02), workload ($F_{28,293}$=6.2; p=.990), and condition by workload effects ($F_{28,293}$=1.56;

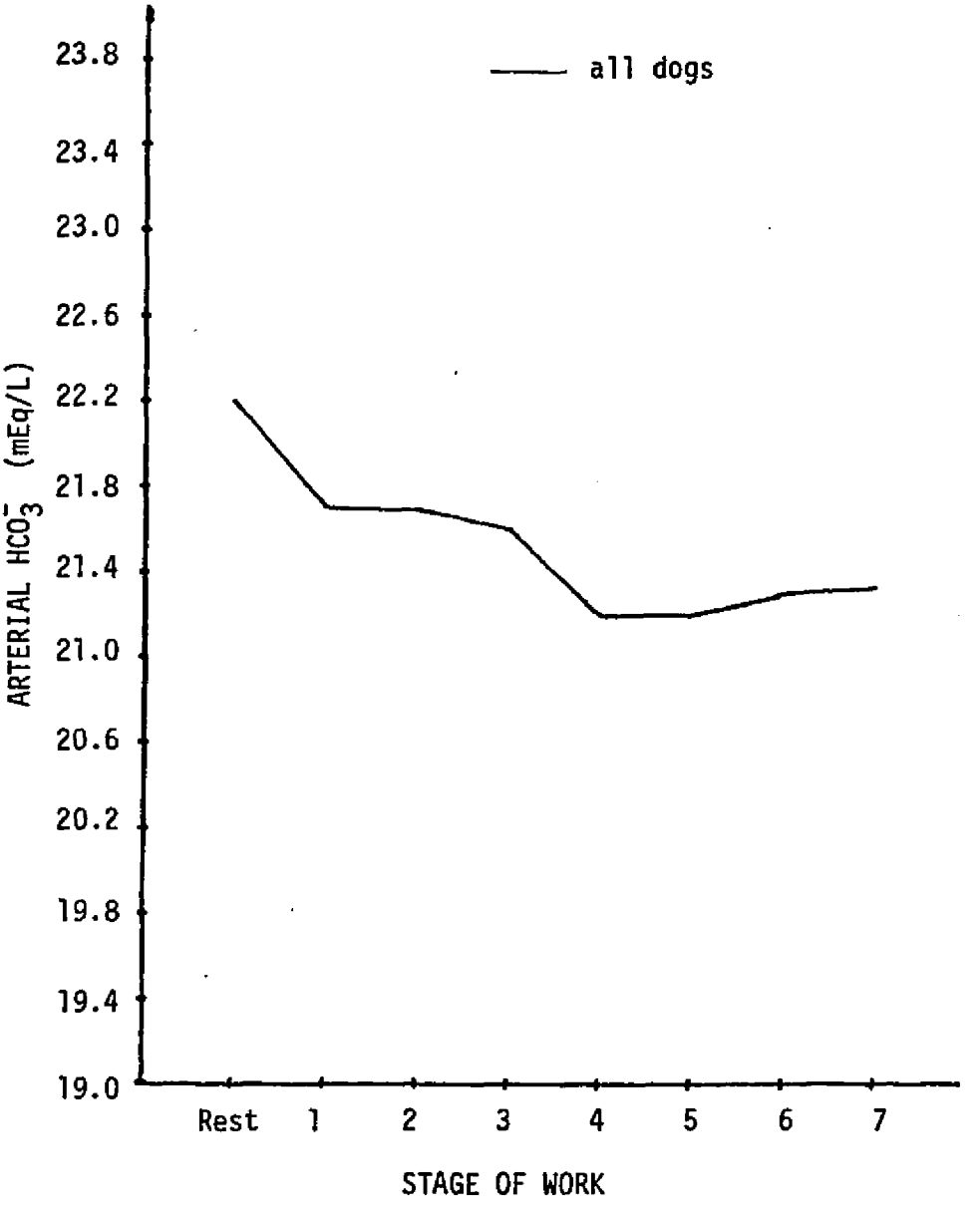

Figure 27. Beta Block vs Normal Exercise: Means of Arterial HCO_3^-

p=.0395) to be significant for venous blood gas and pH.

Venous pH

Beta blockade produced a significant condition effect for venous pH ($F_{1,6}$=19.58; p=.0044). A comparison between resting venous pH levels before and after the infusion of propranolol did not reveal a significant change. The mean venous pH in normal conditions (7.391±.006) was larger than the mean venous pH in beta blocked conditions (7.358±.006). ANOVA did not reveal any significant differences in the venous pH group, group by condition, workload, group by workload, condition by workload, or group by condition by workload effects (Table E-7). The paired t-tests for the transition to exercise and for the highest workload were not significant (Tables E-24 & E-25).

Venous PCO_2

Exercise elicited a significant workload effect ($F_{7,84}$=2.74; p=.0131) on P_vCO_2. Newman-Keuls analysis of the means at each workload identified that most of the P_vCO_2 values were alike. However, w 7's P_vCO_2 was significantly greater than that at w 1. In addition, there were group by workload significant differences for P_vCO_2 ($F_{7,84}$=2.43; p=.0259), which did not show up in the MANOVA for the venous blood gas. The N dogs had a significant rise above their w 1 P_vCO_2 at w 5 (Figure 28). All other P_vCO_2 values for the N dogs were similar. At the same workload (w 5), the CHD dogs had a significant decrease below their w 1 P_vCO_2. All other CHD levels of P_v CO_2 were alike. At w 5, the two groups' P_vCO_2 values were significantly different. Also, the CHD P_vCO_2 at w 5 was significantly lower than the N dogs' P_vCO_2 at w 6 and w 7. While neither group had a significant change in the transition to exercise (Tables E-24 & E-25), both did show a difference in the

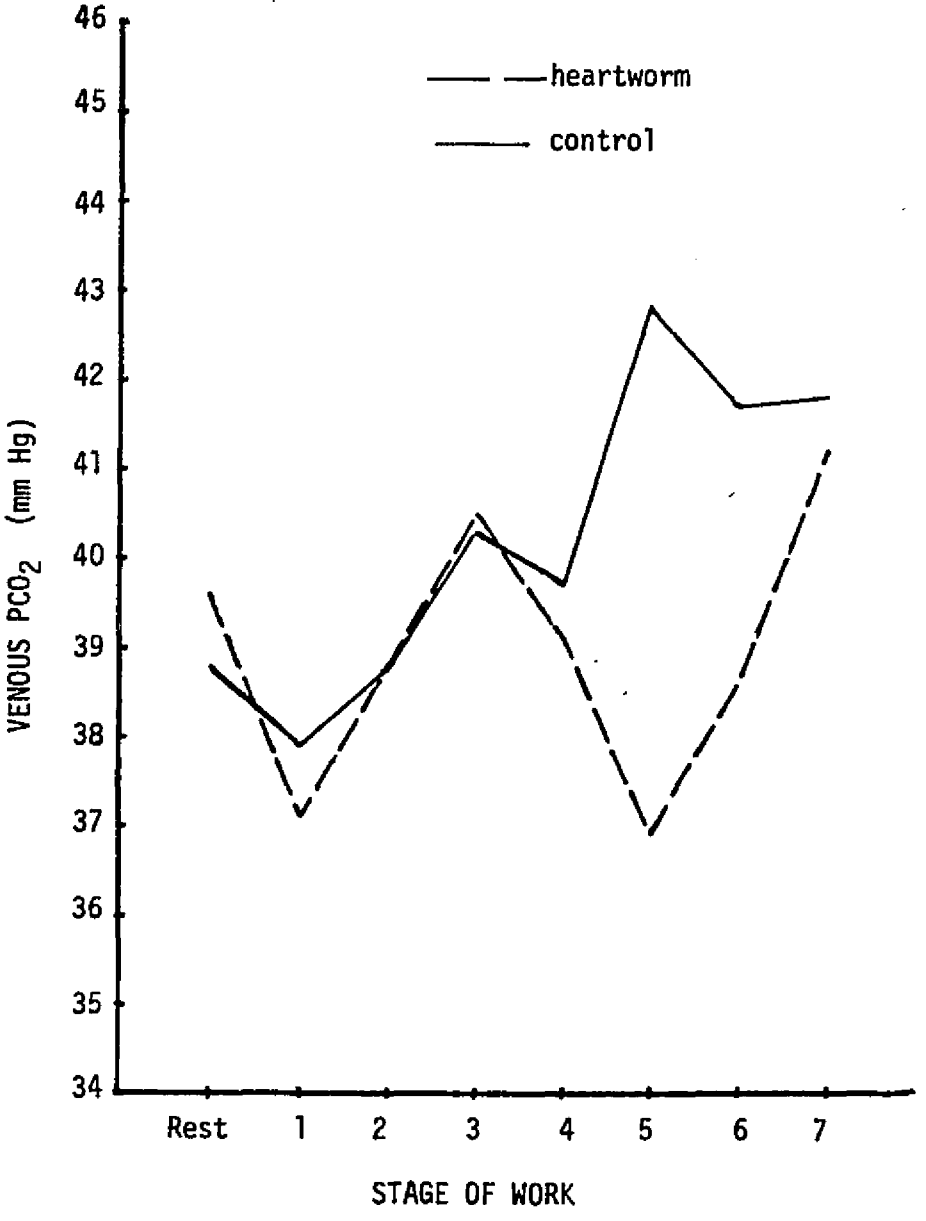

Figure 28. Beta Block vs Normal Exercise: Group Means of Venous PCO_2

comparison between rest and the highest level of stress (CHD: t_3=7.55; p=.9976; N: t_3=6.31; p=.996). The ANOVA did not reveal any significant group, condition, group by condition, condition by workload, or group by condition by workload effects (Table E-8).

Venous PO_2

There was a significant condition effect on P_vO_2 in exercise ($F_{1,6}$=10.75; p=.0168). The t-test for four dogs at rest before and after the propranolol injection was not significant. P_vO_2 during beta blocked conditions (30.1±1.6 mm Hg) was lower than unblocked conditions (34.8±2.3 mm Hg). There were no group, group by condition, group by workload, condition by workload, or group by condition by workload significant effects for P_vO_2 (Table E-9). However, exercise did produce a significant workload effect ($F_{7,84}$=28.2; p=.0001). At the onset of exercise, there was a significant drop in P_vO_2 (Figure 29). The resting P_vO_2 was significantly greater than all exercise values for P_vO_2. The comparison for the transition to beta blocked exercise was not significant in the N dogs. The CHD dogs' values changes significantly at the onset of work following propranolol (t_3=-5.23; p=.007). The comparison from rest to w 7 was not significant for the CHD dogs, but was for the N dogs during beta blocked exercise (t_3=-20.81; p=.0001) (Tables E-24 & E-25).

Venous HCO_3^-

There were no significant differences in venous HCO_3^- for the group, condition, group by condition, workload, group by workload, condition by workload, or group by condition by workload effects (Table E-10). The comparisons during beta blockade from rest to w 1 and from rest to w 7 were not significant in either group of dogs (Tables E-24 &

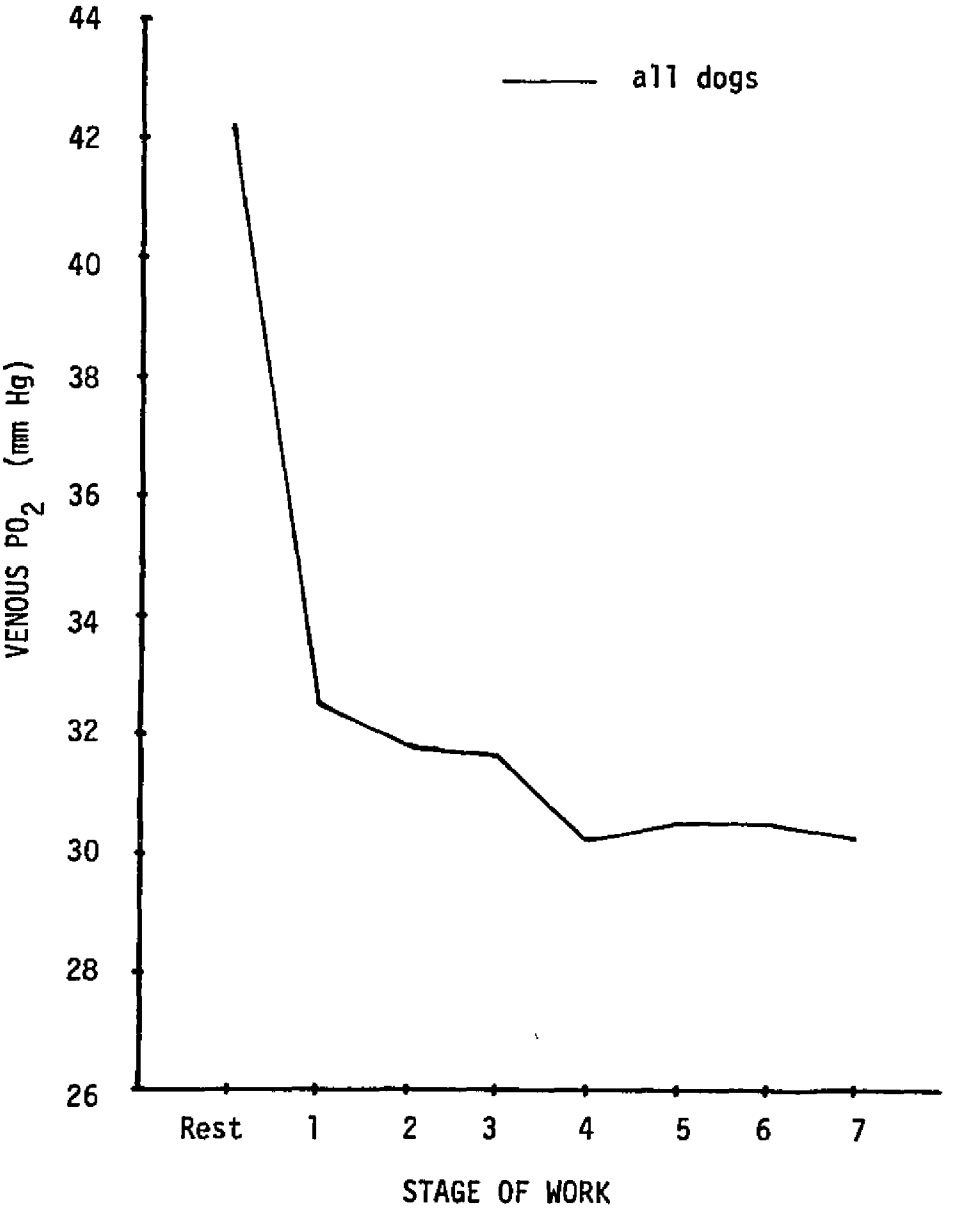

Figure 29. Beta Block vs Normal Exercise: Means of Venous PO_2

E-25).

Discussion

Sham Infusion Exercise

During the sham infusion experiment, the mean T_r was .4° C lower than the mean T_r measured under normal conditions. However, across time, from rest through the last workload, the response of the T_r to incremental work was the same. No data point during the normal exercise test was different from the sham infusion data at the same measurement. The fact that beagles' mean body temperature was a little lower during one test compared to the other may have been an influence of a normal variation, and not related to the infusion vehicle.

K^+ during the sham infusion experiment was only 0.10 mEq/L greater than normal conditions. However, that small diference was significant. The infusion vehicle itself did not produce a change at rest. On the day of the sham infusion, the K^+ levels were insignificantly higher at rest (4.74±.27 vs 4.67±.15 mEq/L). Also, at each workload, there was no significant difference between the K^+ levels during the normal run and the sham infusion run. From rest to w 1, the gain was 7.6% in both tests. At the highest workload, the gain from rest was 10% in the sham infusion run and 14% in the normal run. However, the K^+ values at w 7 during the two different tests were not significantly different. The small significant difference revealed may well be the result of normal daily physiological variation and should not interfere with the influence of beta blockade.

Beta Blocked Exercise

Lactate

The La produced in the muscle of a dog in normal exercise can be used by those muscles for fuel and by the liver to form glucose. In addition, exercise increases the metabolic clearance rate of La in dogs. Hepatic gluconeogenesis used three times as much La during exercise as during rest (Issekutz, Shaw, & Issekutz, 1976). Beta blockade caused reduced liver blood flow at rest and during exercise in dogs (Dumont et al., 1984). During beta blocked exercise in humans, blood flow to the liver decreased, causing liver uptake of La to decrease (Katz, Sahlin & Juhlin-Dannfelt, 1985). With a decreased liver uptake of La, peak La during beta blocked exercise rose significantly above the peak La observed in normal exercise (Powers, Dodd, O'Malley and Brooks, 1984; Katz et al., 1985). Based on human information, one might predict a greater peak La in dogs performing beta blocked exercise. However, propranolol has been shown to inhibit La production in exercising dogs (Issekutz, 1984) by inhibiting muscle glycogenolysis (Issekutz, 1978). Peak exercise La levels in beta blocked dogs have not been found to be higher than those in non-blocked dogs (Barnard & Foss, 1969; Brzezinska & Nazar, 1970).

In the present study, La levels during beta blocked exercise were not different from the La levels during normal exercise. This was contrary to the findings of Cronin (1967), who reported that the rise in La during moderate exercise was eliminated by beta blockade. Barnard and Foss (1969) and Brzezinska and Nazar (1970) both found an increment in La during short, high intensity exercise (19 min and 12 min duration,

respectively) after beta blockade. However, in those two studies, the peak La was significantly lower than the peak La during normal exercise. In the present study, the peak La in normal exercise (1.62±.36 mMol/L) was not significantly greater than the peak La in the beta blocked exercise (1.45±.60 mMol/L), which does not agree with the results of Barnard and Foss (1969) or Brzezinska and Nazar (1970). Different exercise test protocols were used, which may have contributed to some of the varied results. This study used an incremental treadmill exercise test, whereas most of the other studies used one preset speed (range 3-14.4 km/h) and elevation (range 0-20%) for the duration of the exercise test. Some studies involved long runs, greater than 2 h (Brzezinska & Nazar, 1970; Issekutz, 1978, 1984; Issekutz, Shaw & Issekutz, 1976). The short exercise tests took less time than the present study (Barnard & Foss, 1969; Brzezinska & Nazar, 1969; Dumont et al., 1984), except the study by Cronin (1967), which was 24 min long. In order to see a significant inhibition of the La levels in the dogs, perhaps the test would need to be extended to a maximal exercise test. A maximal exercise test might also reveal if any differences exist between the La levels of CHD dogs and N dogs. The anticipated differences between CHD dogs and N dogs were not evident in either unblocked or beta blocked exercise.

Glucose

Beta blockade affects carbohydrate metabolism in that it causes an increase in Glu production, use, and clearance rate (Issekutz, 1978, 1984). During beta blockade, hepatic production of Glu doubled. In beta blocked exercise, 90% of the La produced originated from plasma Glu, which was twice the amount converted to La in normal exercise (Issekutz, 1978, 1984). Although an increase in FFA normally accompanies physical

activity facilitating the rate of uptake of glucose from plasma, FFA dropped during beta blocked exercise (Brzezinska & Nazar, 1969; Cronin, 1967). The ability of the exercising muscle to take up plasma Glu is further enhanced because beta blockade inhibits muscle glycogenolysis, which reduces the amount of available glucose-6-phosphate. The metabolic clearance of plasma Glu during beta blocked exercise was three times the rate of that during unblocked exercise (Issekutz, 1978, 1984).

In the present study, beta blockade caused a small, but significant increase in resting plasma Glu levels. However only the Glu data of two dogs from each group were included in analysis, which may have prevented revelation of differences caused by heartworm disease. No significant Glu changes during beta blocked exercise were discovered in this study, supporting the findings of previous reports (Brzezinska & Nazar, 1969; Cronin, 1967), but disagreeing with Barnard and Foss (1969), who reported small decrements in exercise levels of Glu following beta blockade.

Electrolytes

Sodium

In agreement with Snyder et al. (1967), the CHD dogs did have lower Na^+ levels. However, these differences are very small and within the normal range. In exercise, the N dogs displayed a small, but significant increment (1.5%) in Na^+ about midway through the submaximal exercise test. This increase lends support to two human studies. After one minute of maximal exercise, Sejersted et al. (1982) reported a 7% increase in Na^+ above the resting value. During incremental exercise to exhaustion, there were small but significant increases in Na^+ in humans

tested on a cycle ergometer (Coester, Elliott, & Luft, 1973). The CHD dogs' Na^+ levels did not change from normal exercise when propranolol was administered prior to exercise.

Potassium

Beta blockade produced significantly greater resting K^+ values than recorded in unblocked conditions, which was unlike the findings of Carlsson et al. (1978) and Staib et al. (1980). Typically, exercise stimulates a rapid, significant increase in K^+, that is accentuated by beta blockade. At each workload in the present study, beta blocked K^+ levels were significantly greater than those at comparable workloads during normal exercise. Augmented K^+ levels following beta blockade have been reported in exercise studies using limb preparations (Hirche, Schumacher & Hagemann, 1980; Kjellmer, 1965), dogs running on a treadmill (Staib et al., 1980) and humans cycling (Carlsson et al., 1978; Fellenius, 1983). The results of the present study help support the theory that the blockade of beta adrenergic receptors permits increased stimulation of the alpha receptors and inhibition of the beta mediated uptake of K^+ in nonworking muscle.

In both groups of dogs, beta blockade before exercise produced some increases in K^+ levels. During exercise without beta blockade, the CHD dogs had consistently, but insignificantly higher K^+ levels than did the N dogs. This was also true during beta blocked exercise, with the exception that at w 7, the CHD dogs' K^+ was significantly greater than the N dogs' K^+ at that same workload. At this point, the CHD dogs' K^+ level (5.9+.4 mEq/L) was at the upper limits of normal (5.8 mEq/L).

Catecholamines interact with the adrenergic receptors to stimulate the release (alpha receptor) or uptake (beta receptor) of K^+. Beta

blockade has been shown to inhibit the uptake of K^+ by Na^+/K^+ AtPase (Staib et al., 1980), preventing the catecholamines from interacting with the beta receptors. Without the competition of the beta adrenergic receptors, the action of the alpha adrenergic receptors is basically unopposed. In addition, there are greater quantities of circulating catecholamines during beta blocked exercise than during nonblocked exercise (Staib et al., 1980). Dogs suffering from DI develop an enhanced alpha adrenergic receptor sensitivity (O'Malley et al., 1985). If a CHD dog has enhanced alpha receptors under normal circumstances, it is possible that a N dog during beta blockade may show a similarities to an unblocked CHD dog. Comparing the CHD dogs' unblocked exercise test with the beta blocked exercise of the N dogs, the K^+ levels are qualitatively the same at rest and at each respective workload. It would appear that the results of exercise K^+ values lend support to the enhanced alpha receptor sensitivity in CHD dogs.

Chloride

The Cl^- responses during beta blocked exercise were similar to the responses during unblocked exercise. Propranolol did not affect the Cl^- responses within each group of dogs, but did elicit different levels across work. The N dogs Cl^- data concurred with that of humans (Coester et al., 1973), which showed a small but significant increase at the end of exercise, unlike the CHD dogs in this study. Any influence that CHD might exert on Cl^- levels is difficult to interpret because of the involvement of Cl^- in buffering systems and CO_2 transport. Beta blockade did not change the responses of Cl^- in this exercise study.

Other Physiological Parameters

Hematocrit

During exercise with propranolol, the Hct increased with each workload, as seen during unblocked exercise. Because splenic contraction is alpha mediated, beta blockade was not expected to interfere the increase of Hct in exercising dogs. While there was a significant group by workload interaction, the CHD dogs' Hct at rest and at each level of exercise and the N dogs' Hct at rest and at each exercise workload were qualitatively the same. The significant difference can be attributed to the initial response of the two groups. At w 1, the quantitative difference in the two groups' resting Hct values was eliminated, because the CHD dogs had an 11% gain in their Hct value, while the N dogs only had a 4% gain at the onset of exercise. It is possible that the CHD dogs' alpha receptor hypersensitivity accounted for the 7% greater gain at the onset of exercise. The total gain from resting Hct values measured at the w 7 was similar in both groups (CHD:17% & N:15%).

Rectal Temperature

Both exercise tests elicited similar progressive increments in T_r from rest through the last workload. The beta blocked T_r was slightly elevated above the T_r during the normal exercise experiments, in agreement with Barnard and Foss (1969). During the beta blocked test, the dogs' initial T_r was slightly higher at rest than that during the normal test, which could be the reason for the difference. Because propranolol tends to decrease whole body $\dot{V}O_2$ (Cronin, 1967) and calorigenesis (Goodman & Gilman, 1985), the T_r difference was probably due to daily variations.

Heart Rate

Beta blockade did not significantly change resting HR, supporting the data of Ohyagi, Sasayama, Nakamura, Lee, Kihara, and Kiwai (1984) and Yin, Weisfeldt, and Milnor (1981). However, these results contradict Heyndrickx et al. (1980), who saw a significant reduction in resting HR. The effects of propranolol on HR were best seen during exercise. Beta blockade affected both groups' exercise HR similarly. At each workload, HR was significantly lower than the HR at the same workload during normal exercise, concurring with general findings previously reported in literature (Atkins & Horwitz, 1977; Bassenge et al., 1972; Cronin, 1967; Dumont et al., 1984; Heyndrickx et al., 1980; Ohyagi et al., 1984). At the onset of normal exercise, there was an average increase in HR of 66%, while it was only 37% at the beginning of beta blocked exercise. The total gain at the final stage of beta blocked exercise was about half the total gain during unblocked exercise. The propranolol impaired the adaptation to exercise and shifted the HR response curve downward.

As described for normal exercise HR in Chapter II, the CHD had greater gains in HR than the N dogs at the onset of exercise and at the higest level of stress compared to resting HR. This same pattern was maintained during beta blocked exercise. The CHD dogs had a 26% greater gain above resting HR at w 1 and was 29% higher at w 7 than the N dogs. In both groups of dogs, the decreased HR during beta blockade served to reduce the work of the heart, which would lower the myocardial oxygen demand. A slower HR lengthens the filling time and increases SV (Bassenge et al., 1972). Horwitz et al. (1974) reported an increased end diastolic diameter in mild and moderate beta blocked exercise in dogs. But due to a reduction of the myocardial force of contraction

induced by propranolol, end systolic diameter increased. SV would not be increased as much as during nonblocked moderate exercise (Yin et al., 1981). The CHD dogs have an additional limitation in the ability to increase SV, an increased right ventricular afterload. They must still rely more on HR gains to augment $\dot{Q}$ during exercise, which was evident by the greater gains from resting HR at the transition to work and at the highest stress of the exercise test. They apparently did not adapt to the exercise as easily as the N dogs.

Mean Arterial Blood Pressure

The significant group by workload interaction included the average of both the unblocked and beta blocked data. Therefore, the beta blockade responses muted the data from the normal exercise test for each group. Only the CHD dogs had a significant increment at the onset of exercise that persisted throughout the test. This averaged data does indicate that the CHD dogs had a far greater pressor response at the onset of exercise in both blocked and unblocked tests. The difference in gains above resting MABP in normal exercise were described in Chapter II. The beta blocked data revealed a similar trend, in that the heartworm dogs had greater gains in MABP than the control dogs during the transition to work (12%) and from rest to the highest level of work (12%). The CHD dogs were apparently having an increased pressor response compared to the N dogs. The higher systemic pressures should be an indication of higher systemic resistance. The vasoconstriction of the vessels in nonexercising areas is caused by alpha adrenergic stimulation. During beta blocked exercise, the alpha receptor action might be enhanced without the opposing beta receptor action and with greater levels of circulating catecholamines (Staib et al., 1980). With

an enhanced alpha sensitivity to norepinephrine (O'Malley et al., 1985), the CHD dogs would have more vasoconstriction and greater systemic pressures than the N dogs. It is entirely possible that the CHD dogs' exaggerated pressor response at the onset of exercise is an indication of a compensatory mechanism to improve its ability to perform work. The CHD dog cannot increase its SV as much as a N dog because of pulmonary vascular limitations. Adjustments to increase $\dot{Q}$ can be made by increasing HR. To provide more flow to the muscles, perhaps the dog with heartworms reduces flow to nonworking areas more than healthy dogs would. The enhanced alpha receptor sensitivity in CHD dogs could explain their control mechanisms involved in greater pressor responses to the onset of work.

Propranolol diminished the MABP response during exercise in both groups. During exercise after beta blockade, there were significantly lower systemic arterial pressures, which were not qualitatively different from beta blocked resting MABP. At each workload, these exercise MABP values were similar to those measured during normal exercise at the same workload. The significant rise in pressure in unblocked exercise was not seen at w 1 in beta blocked exercise. The propranolol inhibited exercise response in MABP in this study agrees with previous reports (Atkins & Horwitz, 1977; Bassenge et al., 1972; Ohyagi et al., 1984).

Blood Gas and pH

It has been reported that beta blockade will not affect the ventilatory transient responses at the onset of exercise in the dog (Favier, Desplanches, Frutoso, Grandmontagne, & Flandrois, 1983). A

hyperventilatory response noted in the normal exercise in this study was also seen in the beta blocked experiment. With the onset of exercise, there were rapid increments in arterial pH and decrements in P_aCO_2. These immediate changes were indicative of a respiratory alkalosis which persisted throughout exercise. Beta blockade did not produce any differences in the response to exercise for these two variables, which concurs with the findings of Cronin (1967). Both groups had a similar response during both normal and beta blocked exercise, however only the CHD dogs had significant changes at the transition to work. In normal exercise, the CHD dogs' changes in arterial pH and P_aCO_2 were about three times the N dogs' changes from rest to w 1. Beta blockade actually reduced that difference. During beta blocked exercise, there was only twice the change of the N dogs'arterial pH and P_aCO_2 for the CHD dogs at the onset of exercise.

Propranolol produced a decrease in venous pH. This has not been reported previously. Venous PCO_2 has been shown to rise with increasing work, but in some cases there was little change from resting values (Wathen et al., 1962). When all the exercise data was considered, regardless of condition or group, the only significant increase occurred later in work at w 7. This very small increase reflects some of the results in Wathen et al.'s study (1962). The two groups had different P_vCO_2 responses to exercise at w 5, where the N dogs had a higher P_vCO_2 than the CHD dogs. The beta blockade did not affect the P_vCO_2, contradicting Brundin (1978), who found propranolol increased the P_vCO_2 during exercise.

The 1.0 mEq/L change in arterial HCO_3^- was probably a small transient change at w 4. There was no concommitant rise in La, that

would be indicative of an OBLA.

CHD dogs had lower P_aO_2 than the N dogs, but P_vO_2 values were similar. Beta blockade produced greater P_aO_2 than measured under normal conditions, with changes occurring only in the CHD group. Both groups displayed a decrease in P_vO_2 after propranolol. Without measuring Hb, the O_2 content of arterial and venous blood cannot be determined. However, these dogs probably had a greater a-v O_2 difference during beta blocked conditions compared to normal conditions. Several propranolol studies have reported increased a-v O_2 difference without changes in arterial O_2 content (Bassenge et al., 1972; Cronin, 1967; Horwitz et al., 1974). Increased myocardial a-v O_2 difference following propranolol has also been reported (Heyndrickx et al., 1979, 1980). Because there is a reduced blood flow during beta blockade, there must be a compensatory improved O_2 extraction to maintain sufficient O_2 supplies. Heyndrickx et al. (1980) felt that a greater myocardial O_2 extraction during reduced myocardial blood flow to meet the same O_2 demand was indicative of enhanced alpha receptor activity during beta blockade.

Exercise did not cause significant changes in P_aO_2, which supports the work of Wathen et al.(1962). However, the groups responded differently to exercise stress. Beta blockade did not change the exercise response in P_aO_2 for either group. At rest and at each workload, the N dogs had significantly greater P_aO_2 values than the CHD dogs at rest and at the same workload. At the onset of work, the P_aO_2 changes were small. The N dogs had a 10% increase above resting values, while the CHD dogs had a 1% decrease. At the final workload, the N dogs had an 11% increment from resting levels, while the CHD dogs' values dropped 6%. Venous PO_2 was also affected by exercise. There was a

rapid response at the onset of exercise, with P_vO_2 significantly lower than rest. Throughout the rest of the exercise test, the reduced values were maintained, which concurs with Wathen et al. (1962). The initial decrement was greater in the CHD dogs (31%) than in the N dogs (22%). At the highest level of work, both groups had similar decreases from their resting values (31%). During exercise, a-v O_2 difference increases linearly with increasing work (Walthen et al., 1962). During beta blocked exercise, there are even greater a-v O_2 differences, except during severe exercise (Horwitz, et al., 1974). Walthen et al. (1962) found that the changes in arterial and venous PO_2 were proportional to the changes in arterial and venous O_2 content. Had Hb been measured, the greater a-v O_2 difference at each workload probably would have been revealed. Theoretically, these differences would have been enhanced during beta blockade.

Summary

Propranolol (2 mg/kg) was administered before exercise to block the beta adrenergic receptors in dogs with heartworm disease and in dogs without heartworm disease. Beta blockade exercise produced similar responses as normal exercise in La, N^+, Cl^-, Hct, arterial pH and HCO_3^-, P_aO_2, P_vO_2, and venous pH. Glu, T_r, and K^+ were increased during the beta blocked conditions, while venous pH and P_vO_2 were decreased. In the CHD dogs, beta blockade increased P_aO_2. During beta blocked exercise, K^+ levels at each workload were greater than observed during normal exercise. As seen in normal exercise, the CHD dogs had consistently, but insignificantly, higher K^+ levels than the N dogs during beta blocked exercise. Beta blockade inhibited the inotropic and

chronotropic effects of the sympathetic nervous system on the heart during exercise, significantly lowering MABP and HR at each workload.

The CHD dogs had more difficulty in adapting to beta blocked exercise, indicated by greater gains in HR and MABP at the onset of exercise. The respiratory alkalosis due to hyperventilation at the onset of beta blocked exercise was greater in the CHD dogs, suggesting a dyspnea during the transition to exercise. Contributing support to the theory of enhanced alpha receptor sensitivity in CHD dogs were the greater increments in Hct and K^+ at the beginning of work. Further study of the alpha adrenergic involvement in the pathogenesis of heartworm disease would be beneficial.

Chapter IV

CONCLUSIONS

A dog with heartworm disease may not have any visible signs of the disease at rest, particularly in the earlier stages of the disease. A reduced exercise tolerance is one of the signs of heartworm disease. In order for a dog to perform exercise, it needs to increase $\dot{Q}$. Pathophysiological changes in the pulmonary vasculature interfere with the CHD dog's ability to increase $\dot{Q}$ during exercise. These dogs will have to compensate for those limitations. For example, an increased HR can augment $\dot{Q}$ when SV does not increase. A dog with moderate or mild heartworm disease may be able to complete a submaximal exercise test without noticeable difficulty. To achieve this, are there some mechanisms at work in the heartworm dog that would compensate for problems, such as lower P_aO_2 and pulmonary limitations to flow? In this study, the submaximal exercise responses of four dogs with heartworm disease and no contraindications to exercise were compared to those of four control dogs. In dogs classified as having moderate CHD, many responses to submaximal exercise were qualitatively the same in a number of variables. With increases in workload, there were progressive increments in T_r, HR, and Hct. MABP, and K^+ displayed a rapid increase in the beginning of exercise. These augmented levels were maintained throughout the exercise test. Respiratory alkalosis was evident in the first three min of exercise. The CHD dogs displayed signs of exaggerated

pressor responses to exercise, and had larger increments in K^+ and Hct at the onset of exercise. These differences provide evidence for an enhanced alpha receptor activity in the CHD group during the transition to exercise. They also had greater initial respiratory alkalosis, and were functioning with lower P_aO_2 levels. It was suggested before the study that heartworm dogs might need to supplement the aerobic metabolism with anaerobic metabolism in incremental treadmill exercise earlier than healthy dogs would. This would be indicated by having an OBLA at a lower workload than the control dogs. Perhaps, this might be a means of compensating for lower O_2 in the blood. However, neither group showed clear evidence of an OBLA and their La levels were similar.

In the second portion of the study, beta adrenergic blockade was achieved with propranolol, administered prior to the submaximal exercise test. Beta blockade inhibited inotropic and chronotropic effects of the sympathetic nervous system on the heart. Once again, the CHD dogs had an exaggerated pressor response, and greater gains in Hct and K^+ at the onset of exercise. These differences may indicate a compensatory mechanism in the CHD dogs to increase flow to working muscles despite the right ventricular overload associated with heartworm disease. It is also possible that the CHD dogs may have an improved O_2 extraction to compensate for lower P_aO_2 levels. In order to test for increased a-v O_2 differences, it would be necessary to measure Hb and the partial pressure of oxygen to calculate O_2 content in the arterial and venous bloods. Future research should address the O_2 extraction during exercise in dogs with heartworm disease. To investigate possible adrenergic imbalance in these dogs, an alpha blockade study would help identify the contribution of the alpha adrenergic system during a time

of exercise stress. Through additional research, it may be possible to clarify and identify compensatory mechanisms used in dogs with *Dirofilaria immitis* to perform exercise.

REFERENCES

References

Astrand, P. O. (1981). Aerobic and anaerobic energy sources in exercise. In: Medicine Sport: vol. 13, (pp. 22-37). Karger:Basel.

Astrand, P. O., & Rodahl, K. (1977). Textbook of Work Physiology. New York: McGraw-Hill.

Atkins, J. M., & Horwitz, L. D. (1977). Cardiac autonomic blockade in exercising dogs. Journal of Applied Physiology, 42, 878-883.

Badke, F. R. (1984). Left ventricular dimensions and function during exercise in dogs with chronic right ventricular pressure overload. American Journal of Cardiology, 53, 1187-1193.

Barger, A. C., Richards, J., Metcalfe, J., & Gunther, B. (1956). Regulation of the circulation during exercise. Cardiac output (direct Fick) & metabolic adjustments in the normal dog. American Journal of Physiology, 184, 613-623.

Barnard, R. J., & Foss, M. L. (1969). Oxygen debt: effect of beta-adrenergic blockade on the lactacid and alactacid components. Journal of Applied Physiology, 27, 813-816.

Barnes, C. D., & Etherington, L. G. (1975). Drug Dosage in Laboratory Animals. A Handbook. Berkeley: University of Ca. Press.

Barsanti, J. A., Kristensen, F., & Drumheller, F. B. (1977). Analysis of serum proteins, using agarose electrophoresis in normal dogs & in dogs naturally infected with *Dirofilaria immitis*. American Journal of Veterinary Research, 38, 1055-1058.

Bassenge, E., Kucharczyk, M., Holtz, J., & Stoian, D. (1972). Treadmill exercise in dogs under *B*-adrenergic blockade: Adaptation of coronary and systemic hemodynamics. Pflugers Archives, 332, 40-55.

Bhargava, R. K. (1973). Cor Pulmonale (Pulmonary Heart Disease). Mount Kisco, NY: Futura Publ. Co.

Bisgard, G. E., Orr, J. A., Ungerer, T., & Will, J. A. (1972). Effect of training upon pulmonary & systemic hemodynamics in beagle dogs. Laboratory Animal Science, 22, 72-76.

Bove, A. A., Hultgren, P. B., Ritzer, T. F., & Carey, R. A. (1979) Myocardial blood flow and hemodynamic responses to exercise training in dogs. Journal of Applied Physiology, 46, 571-578.

Brill, I. C. (1957). Cor pulmonale: A semantic consideration with brief notes on diagnosis & treatment. Modern Concepts of Cardiovascular Disease, 26, 425-429.

Brown, H. V., & Wasserman, K. (1981). Exercise performance in chronic obstructive pulmonary disease. Medicial Clinics of North America, 65, 525-547.

Brundin, T. (1978). Effects of B-adrenergic blockade on metabolic rate and mixed venous blood temperature during dynamic exercise. Scandinavian Journal of Clinical Laboratory Investigation, 38, 229-232.

Brzezrinska, A., & Nazar, K. (1970). Effect of Beta-adrenergic blockade on exercise metabolism in dogs. Archives Internationales de Physiologie et de Biochimie, 78, 883-892.

Buono, M. J., Clancy, T. R., & Cook, J. R. (1984). Blood lactate and ammonium ion accumulation during graded exercise in humans. Journal of Applied Physiology, 57, 135-139.

Cain, S. M. (1970). O_2 uptake during & after exercise with & without β-adrenergic blockade. Federation Proceedings, 29, 265 Abs (#112).

Calvert, C. A., & Rawlings, C. A. (1983). Diagnosis & management of canine heartworm disease. In R. W. Kirk (Ed.), Current Veterinary Therapy VIII: Small Animal Practice (pp. 348-359). Philadelphia: W. B. Saunders Co.

Calvert, C. A., & Rawlings, C. A. (1985). Pulmonary manifestations of heartworm disease. Veterinary Clinics of North America: Small Animal Practice, 15, 991-1009.

Carlsson, E., Fellenius, E., Lundborg, P., & Svensson, L. (1978). β-adrenoceptor blockers, plasma-potassium, & exercise. The Lancet, 2, 424-425.

Cerretelli, P., Piiper, J., Mangili, F., & Ricci, B. (1964a). Aerobic and anaerobic metabolism in exercising dogs. Journal of Applied Physiology, 19, 25-28.

Cerretelli, P., Piiper, J., Mangili, F., Cuttica, F., & Ricci, B. (1964b). Circulation in exercising dogs. Journal of Applied Physiology, 19, 29-32.

Coester, N., Elliott, J. C., & Luft, U. C. (1973). Plasma electrolytes, pH, and ECG during and after exhaustive exercise. Journal of Applied Physiology, 34, 677-682.

Cori, C. F., & Cori, G. T. (1929). Glycogen formation in the liver from d- and l-lactic acid. Journal of Biological Chemistry, 81, 389-403.

Cronin, R. F. (1967). Hemodynamic and metabolic effects of beta-adrenergic blockade on exercising dogs. Journal of Applied Physiology, 22, 211-216.

Dampney, R. A. L. (1974). Cardiovascular alterations associated with bursts of panting in the exercising dog. Journal of Physiology, 238, 17-36.

Dejours, P. (1966). Respiration. New York: Oxford Univ. Press.

Dejours, P. (1981). Principles of comparative respiratory physiology (2nd rev. ed.). New York: Elsevier.

Depocas, F., Minaire, Y., & Chatonnet, J. (1969). Rates of formation and oxidation of lactic acid in dogs at rest and during moderate exercise. Canadian Journal of Physiology and Pharmacology, 47, 603-610.

Donald, D. E. & Ferguson, D. (1966). Response of heart rate, oxygen consumption, and arterial blood pressure to graded exercise in dogs. Proceedings of the Society of Experimental Biology & Medicine, 121, 626-630.

Donovan, C. M., & Brooks, G. A. (1983). Endurance training affects lactate clearance, not lactate production. American Journal of Physiology, 244 (Endocrinology Metabolism 7), E83-E92.

Dumont, L., Magrassi, P., Parent, R., Stanley, P. & Chartrand, C. (1984). Effects of propranolol & exercise on cardiac dynamics & organ blood flow distribution in dogs. Journal of Autonomic Pharmacology, 4, 251-256.

Ettinger, S. F., & Suter, P.F. (1970). Canine Cardiology (pp. 421-455). Philadelphia: W. B. Saunders Co.

Favier, R., Desplanches, D., Frutuso, J., Grandmontagne, M., & Flandrois, R. (1983). Ventilatory transients during exercise: Peripheral or central control? Pflugers Archives, 396, 269-276.

Fellenius, E. (1983). Muscle fatigue & *B*-blockers - A review. International Journal of Sports Medicine, 4, 1-8.

Ferrer, M. I. (1975). Cor pulmonale (pulmonary heart disease): Present-day status. American Heart Journal, 89, 657-664.

Fishman, A. R. (1976). Chronic cor pulmonale. American Review of Respiratory Diseases, 114, 775-794.

Fixler, D. E., Atkins, J. M., Mitchell, J. H., & Horwitz, L. D. (1976). Blood flow to respiratory, cardiac, & limb muscles in dogs during graded exercise. American Journal of Physiology, 231, 1515-1519.

Gay, W. I. (1984). The dog as a research subject. The Physiologist, 27, 133-141.

Gladden, L. B. (1984). Current "anaerobic threshold" controversies. The Physiologist, 27, 312-318.

Goldberg, M. B., Langman, V. A., & Taylor, C. R. (1981). Panting in dogs: Paths of air flow in response to heat and exercise. Respiration Physiology, 43, 327-338.

Gollnick, P. D., & Hermansen, L. (1973). Biochemical adaptations to exercise: anaerobic metabolism. In J. H. Wilmore (Ed.), Exercise & Sport Science Reviews: vol. 1 (pp. 1-43). New York: Academic Press.

Gilman, A. G., Goodman, L. S., Rall, T. W., & Murad, F. (Eds.). (1985). Goodman and Gilman's The Pharmacological Basis of Therapeutics (7th ed.). New York: Macmillan Publishing Co.

Graham, T. E. (1984). Mechanisms of blood lactate increase during exercise. The Physiologist, 27, 299-303.

Grieve, R. B., Mika-Johnson, M., Jacobson, R. H., & Cypress, R. H. (1981). Enzyme-linked immunosorbent assay for measurement of antibody response to *Dirofilaria immitis* in experimentally infected dogs. American Journal of Veterinary Research, 42, 66-69.

Guyton, A. C. (1985). Textbook of Medical Physiology (7th ed.). Philadelphia: W. B. Saunders Co.

Heinsimer, J. A. & Lefkowitz, R. J. (1982). Adrenergic receptors: Biochemistry, regulation, molecular mechanism, and clinical implications. The Journal of Laboratory & Clinical Medicine, 100, 641-658.

Herrick, J. F., Grindlay, J. H., Baldes, E. J., & Mann, F. C. (1939). Effect of exercise on the blood flow in the superior mesenteric, renal and common iliac arteries. American Journal of Physiology, 128, 338.

Heyndrickx, G. R., Mabilde, C., & Pannier, J. L. (1979). Effect of propranolol on myocardial oxygen balance during exercise in dogs. Journal of Physiology (London), 295, 41P.

Heyndrickx, G. R., Pannier, J.-L., Muylaert, P., Mabilde, C., & Leusen, I. (1980). Alteration in myocardial oxygen balance during exercise after β-adrenergic blockade in dogs. Journal of Applied Physiology, 49, 28-33.

Hirche, H., Schumacher, E., & Hagemann, H. (1980). Extracellular K^+ concentration and K^+ balance of the gastrocnemius muscle of the dog during exercise. Pflugers Archives, 387, 231-237.

Hirth, R. S., & Nielson, S. W. (1966). Journal of the American Veterinary Medical Association, 149, 915-919.

Holloszy, J. O., & Coyle, E. F. (1984). Adaptations of skeletal muscle to endurance exercise & their metabolic consequences. Journal of Applied Physiology, 56, 831-838.

Hornbrook, K. R. (1970). Adrenergic receptors for metabolic responses in the liver. Federation Proceedings, 29, 1381-1385.

Horwitz, L. D., Atkins, J. M., & Leshin, S. J. (1974). Effect of beta-adrenergic blockade on left ventricular function in exercise. American Journal of Physiology, 227, 839-842.

Hoskins, J. D., Hagstad, H. V., Hribernik, T. N., & Breitschwerdt, E. B. (1984). Heartworm disease in dogs from Louisiana: pretreatment clinical & laboratory evaluation. Journal of the American Animal Hospital Association, 20, 205-210.

Hultman, E., & Sahlin, K. (1981). Acid-base balance during exercise. In R. S. Hutton & D. I. Miller (Eds.), Exercise & Sport Science Reviews: vol. 8, 1980 (pp. 41-128). Philadelphia: Franklin Institute.

Issekutz, Jr., B. (1978). Role of the beta-adrenergic receptors in mobilization of energy sources in exercising dogs. Journal of Applied Physiology, 44, 869-876.

Issekutz, Jr., B. (1984). Effect of β-adrenergic blockade on lactate turnover in exercising dogs. Journal of Applied Physiology, 57, 1754-1759.

Issekutz, Jr., B., Shaw, W. A. S., & Issekutz, A. C. (1976). Lactate metabolism inresting and exercising dogs. Journal of Applied Physiology, 40, 312-319.

Jackson, R. F., Otto, G. F., Bauman, P. M., Peacock, F., Hinrichs, W. L., & Maltby, J. H. (1966). Distribution of heartworms in the right side of the heart & adjacent vessels of the dog. Journal of the American Veterinary Medical Association, 149, 515-518.

Jackson, W. F. (1969a). Physical examination of heartworm-infected patients. Journal of Veterinary Medical Association, 154 (4), 377-378.

Jackson, W. F. (1969b). Radiographic examination of the heartworm-infected patient. Journal of the American Veterinary Medical Association, 154 (4), 380-382.

Jennings, D. B., Phillips, H. H., Chen, C. C., & Sparling, J. (1973). Cardiovascular function in panting and nonpanting resting conscious dogs. American Journal of Physiology. 224, 1059-1065.

Jones, N. L., & Ehrsham, R. E. (1982). The anaerobic threshold. In J. H. Wilmore (Ed.), Exercise & Sport Science Review: vol. 10 (pp.49-83). New York: Academic Press.

Katz, A., Sahlin, K., & Juhlin-Dannfelt, A. (1985). Efeect of β-adrenergic blockade on H^+ and K^+ flux in exercising humans. Journal of Applied Physiology, 59, 336-341.

Khaja, F., & Parker, J. O. (1971). Right and left ventricular performance in chronic obstructive lung disease. American Heart Journal, 82, 319-327.

Kirk, R. W. (Ed.) (1983). Current Veterinary Therapy, VIII: Small Animal Practice. Philadelphia: W. B. Saunders Co.

Kjellmer, I. (1965). The potassium ion as a vasodilator during muscular exercise. Acta Physiologica Scandinavia, 63, 460-468.

Knauer, K. W. (1978). Heartworm Disease. Unpublished manuscript, Texas A & M University, College Station.

Knight, D. H. (1968a). Efects of Chronic *Dirofilaria immitis* infestations on cardiopulmonary dynamics & right ventricular activation in the dog. 18th Gaines Veterinary Symposium, 15-23.

Knight, D. H. (1968b). Effects of spontaneous cor pulmonale (*Dirofilaria immitis* infestation) on the gross morphology & hemodynamics of the lung circulation & ventricles. Unpublished master's thesis, Univ. of Pennsylvania, Philadelphia.

Knight, D. H. (1974). Pulmonary complication of dirofilariasis. In R. W. Kirk (Ed.), Current Veterinary Therapy V: Small Animal Practice (pp. 225-227). Philadelphia: W. B. Saunders Co.

Knight, D. H. (1977). Heartworm heart disease. Advanced Veterinary Science Comparative Medicine, 21, 107-149.

Knight, D. H. (1981). Evolution of pulmonary artery disease in canine dirofilariasis: evolution by blood pressure measurements and angiography. In G. F. Otto (Ed.), Proceedings of Heartworm Symposium, '80, (pp. 55-62). Edwardsville, KS: Veterinary Medical Publ. Co.

Kume, S. & Itagski, S. (1955). On the life cycle of *Dirofialria immitis* in the dog as a final host. British Veterinary Journal, 111, 16-24.

Levine, B. G. (1974). Dirofilariasis. In R. W. Kirk (Ed.), Current Veterinary Therapy V: Small Animal Practice (pp. 298-304). Philadelphia: W. B. Saunders Co.

Marshall, R. J., Wang, Y., Semler, H. J., & Shepherd, J. T. (1961). FLow pressure, & volume relationships in the pulmonary circulation during exercise in normal dogs & dogs with divided left pulmonary artery. Circulation Research, 9, 53-59.

Matthay, R. A., & Berger, H. J. (1981). Cardiovascular performance in chronic obstructive pulmonary disease. Medical Clinics of North America, 65, 489-524.

Maxwell, White & Faulkner (1980). Oxidative capacity, blood flow, & capillarization of skeletal muscles. Journal of Applied Physiology, 49, 627-633.

Mills, L. J. & Simmons, D. H. (1967). An arterial catheter for chronic implantation in dogs. Journal of Applied Physiology, 23, 285-286.

Mitchell, J. H., Kaufman, M. P., & Iwamoto, G. A. (1983). The exercise pressor reflex: Its cardiovascular effects, afferent pathways, & central pathways. Annual Review of Physiology, 45, 229-242.

Morgan, H. C. (1969). Laboratory evaluation of the heartworm-infected patient. Journal of the American Veterinary Medical Association, 154 (4), 378-380.

Muir, W. W., & Sams, R. (1984). Clinical pharmacodynamics & pharmacokinetics of Beta-adrenergic blocking drugs in veterinary medicine. The Compendium on Continuing Education for the Practicing Veterinarian, 6, 156-167.

Musch, T. I., Haidet, G. C., Ordway, G. A., Longhurst, J. C., & Mitchell, J. H. (1985). Dynamic exercise training in foxhounds. I. Oxygen consumption & hemodynamic responses. Journal of Applied Physiology, 59, 183-189.

Mutch, B. J. C., & Banister, E. W. (1983). Ammonia metabolism in exercise & fatigue: a review. Medicine & Science in Sports & Exercise, 15, 41-50.

Mylecharane, E. J., & Raper, C. (1973). Further studies on the adrenergic neuron blocking activity on some *B*-adrenoceptor antagonists & guanethidine. Journal of Pharmicological Pharmacology, 25, 213-220.

National Institutes of Health. (1978). Guide for the Care and Use of Laboratory Animals. DHEW Publication No. (NIH) 78-33 Washington, D.C.: U.S. Government Printing Office.

Ohyagi, A., Sasayama, S., Nakamura, Y., Lee, J. D., Kihara, Y., & Kawai, C. (1984). Effect of ICI 118,587 on left ventricular function during graded treadmill exercise in conscious dogs. American Journal of Cardiology, 54, 1108-1113.

Olson, N. C., Scott, J. B., Stoffs, W. V., & Robinson, N. E. (1982). Central blood volume & lung extravascular thermal volume in dogs with dirofilariasis. American Journal of Veterinary Research, 46 (6), 1019-1022.

O'Malley, N. A. (1986). Effect of *Dirofilaria Immitis* on canine cardiopulmonary physiology. (Doctoral dissertation, Louisiana State University School of Veterinary Medicine, 1986).

O'Malley, N. A., Venugopalan, C. S., & Crawford, M. P. (1985). Contractile responses to histamine of isolated pulmonary artery strips from healthy and heartworm-infected dogs. American Journal of Veterinary Research, 46, 1463-1467.

Ordway, G. A., Floyd, D. A., Longhurst, J. C., & Mitchell, J. H. (1984). Oxygen consumption & hemodynamic responses during graded treadmill exercise in dogs. Journal of Applied Physiology, 57, 601-607.

Osborne, T. C. (1847). Worms found in the heart & blood vessels of a dog: Symptoms of hydrophobia. Western Journal of Medicine & Surgery, 96 NS (8), 491-492.

Otto, G. F. (1978). The significance of microfilaremia in the diagnosis of heartworm infection. In G. F. Otto (Ed.) Proceedings of Heartworm Symposium, '77 (pp.22-30). Edwardsville,KS: Veterinary Medical Publ. Co.

Otto, G. F., & Jachowski, L. A. (1981). Mosquitoes & canine heartworm disease. In G. F. Otto (Ed.), Proceedings of Heartworm Symposium, '80 (pp. 17-32). Edwardsville, KS: Veterinary Medical Publ. Co.

Owles, W. H. (1930). Alterations in the lactic acid content of the blood as a result of light exercise and associated changes in the CO_2-combining power of the blood and in the alveolar CO_2 pressure. Journal of Physiology, 69, 214-237.

Parsons, D., Musch, T. I., Moore, R. L., Haidet, G. C., & Ordway, G. A. (1985). Dynamic exercise training in foxhounds. II. Analysis of skeletal muscle. Journal of Applied Physiology, 59, 190-197.

Peronnet, F., Nadeau, R. A., de Champlain, J., Magrassi, P., & Chatrand, C. (1981). Exercise plasma catecholamines in dogs: Role of adrenals and cardiac nerve endings. American Journal of Physiology, 241, 243-247.

Powers, S. K., Dodd, S., O'Malley, N. A., & Brooks, E. (1984). Effects of beta-adrenergic blockade on ventilation and gas exchange during incremental exercise. Manuscript submitted for publication.

Raab, J. L., Eng, P., & Waschler, R. A. (1976). Metabolic cost of grade running in dogs. Journal of Applied Physiology, 41, 532-535.

Rakel, R. R. (Ed.). (1985). 1985 Conn's Current Therapy. Philadelphia: W. B. Saunders Co.

Rawlings, C. A. (1980). Cardiopulmonary function in the dog with *Dirofilaria immitis* infection: during infection & after treatment. American Journal of Veterinary Research, 41 (3), 319-324.

Rawlings, C. A. (1981). Exercise in the dog with *Dirofilaria immitis* infection. American Journal of Veterinary Research, 42, 2057-2060.

Rawlings, C. A. (1982). Clinical laboratory evaluations of seven heartworm infected beagles: During disease development and following treatment. Cornell Veterinarian, 72, 49-56.

Rawlings, C. A., Dawe, D. L., McCall, J. W., Keith, J. C., & Prestwood, A. K. (1982). Four types of occult *Dirofilaria immitis*. Journal of the American Veterinary Medical Association, 180, 1323-1326.

Rawlings, C. A., & Lewis, R. E. (1978). Does heartworm disease produce dilation or hypertrophy of the right ventricle? In G. F. Otto (Ed.), Proceedings of Heartworm Symposium, '77 (76-78), Bonner Springs, KS: Veterinary Medical Publishing Co.

Rawlings, C. A., McCall, J. W., & Lewis, R. E. (1978). The response of the canine's heart & lungs to *Dirofilaria immitis*. Journal of the American Animal Hospital Association, 14, 17-32.

Rawlings, C. A., Prestwood, A. K., & Beck, B. B. (1980). Eosinophilia and basophilia in *Dirofilaria immitis* and *Dipetalenoma reconditum* infections. Journal of the American Animal Hospital Association, 16, 699-704.

Rawlings, C. A., Schaub, R. G., Lewis, R. E., & McCall, J. W. (1981). Heartworm-induced pulmonary vascular lesions: development & resolution. In G. F. Otto (Ed.), Proceedings of Heartworm Symposium, '80 (pp. 63-66). Edwardsville: Veterinary Medical Publ. Co.

Rushmer, R. F., Franklin, D. L., Van Citters, R. L., & Smith, O. A. (1961). Changes in peripheral blood flow distribution in healthy dogs. Circulation Research, 9, 675-687.

Sanders, T. M., Werner, R. A., & Bloor, C. M. (1976). Visceral blood flow distribution during exercise to exhaustion in conscious dogs. Journal of Applied Physiology, 40, 927-931.

Savell, C. M. (1974). The use of circulation time as a diagnostic & prognostic aid in canine heartworm disease. Journal of the American Animal Hospital Association, 10, 499-500.

Sejersted, O. M., Medbo, J. I., & Hermansen, L. (1982). Metabolic acidosis and changes in water and electrolyte balance after maximal exercise. In R. Porter & G. Lawrensen (Eds.), 1982 Metabolic Acidosis (Ciba Foundation Symposium 87) (pp.153-167). London: Pitman Books Ltd.

Sharma, M. C., & Pachauri, S. P. (1982). Blood cellular & biochemical studies in canine dirofilariasis. Veterinary Research Communications, 5, 295-300.

Sigma Technical Bulletin (1968). No. 826-UV.

Skinner, N. S., Jr. & Costin, J. C. (1970). Interactions of vasoactive substances in exercise hyperemia: O_2, K^+, & Osmolarity. American Journal of Physiology, 219, 1386-1392.

Smulyan, H., Cuddy, R. P., Vincent, W. A., Kashemsant, U., & Eich, R. H. (1965). Initial hemodynamic responses to mild exercise in trained dogs. Journal of Applied Physiology, 20, 437-442.

Snyder, J. W., Liu, S-K., Tashjian, R. J. (1967). Blood chemical & cellular changes in canine dirofilariasis. American Journal of Veterinary Research, 28, 1705-1710.

Staib, A. H., Appel, E., Starey, F., Lindner, E., Grotsch, H., Palm, D., & Grobecker, H. (1980). Exercise induced changes of catecholamines & potassium in plasma of dogs after treatment with propranolol. Arzneimittel-forschung/Drug Research, 30, 1514-1517.

Stone, H. L. (1980). Coronary flow, myocardial oxygen consumption, & exercise training in dogs. Journal of Applied Physiology, 49, 759-768.

Stuart, B. P., Hoss, H. E., Root,, C. R., & Short, T. (1978). Ischemic myopathy associated with systemic dirofilariasis. Journal of the American Animal Hospital Association, 14, 36-39.

Strauss, R. H. (Ed.). (1979). Sports Medicine & Physiology. Philadelphia: W. B. Saunders Co.

Szlyk, P. C., McDonald, B. W., Pendergast, D. R., & Krasney, J. A. (1981). Control of ventilation during graded exercise in the dog. Respiration Physiology, 46, 345-365.

Thrall, D. E., Badertscher, R. R., Lewis, R. E., & McCall, J. W. (1979). Scintigraphic evaluation of pulse perfusion in dogs experimentally infected with *Dirofilaria immitis*. American Journal of Veterinary Research, 40, 1426-1432.

Thrall, D. E., Badertscher, R. R., Lewis, R. E., & McCall, J. W. (1979). The pulmonary arterial circulation in dogs experimentally infected with *Dirofilaria immitis*: its angiographic evaluation. Journal of the American Veterinary Radiology Society, 20 (2), 74-78.

Thrasher, P. (1965). Canine dirofilariasis. Veterinary Scope, X(1), 2-24.

Tilley, L. P. (1979). Essentials of canine and feline electrocardiography. St. Louis: C. V. Mosby Co.

Tipton, C. M., Carey, R. A., Eastin, W. C., & Erickson, H. H. (1974). A submaximal test for dogs: evaluation of effects of training, detraining & cage confinement. Journal of Applied Physiology, 37, 271-275.

Van Citters, R. L., & Franklin, D. L. (1969). Cardiovascular performance of Alaska sled dogs during exercise. Circulation Research, 24, 33-42.

Vatner, S. F. (1978). Effects of severe exercise on distribution of cardiac output in conscious dogs. In J. Baan, A. Noordergraaf, & J. Raines (Eds.), Cardiovascular System Dynamics, (pp. 449-457), Cambridge, MA.: MIT Press.

Vatner, S. F., Baig, H., Manders, W. T., Ochs, H., & Pagani, M. (1977). Effects of propranolol on regional myocardial function, electrograms and blood flow in conscious dogs with myocardial ischemia. Journal of Clinical Investigation, 60, 353-360.

Vatner, S. F., Higgins, C. B., Millard, R. W., & Franklin, D. (1974). Role of the spleen in the peripheral vascular response to severe exercise in untethered dogs. Cardiovascular Research, 8, 276-282.

Vatner, S. F., & Pagani, M. (1976). Cardiovascular adjustments to exercise: Hemodynamics & mechanisms. Progress in Cardiovascular Diseases, XIX, 91-108.

Wagner, J. E., Horvath, S. M., & Dahms, T. E. (1977). Cardiovascular, respiratory, & metabolic adjustments to exercise in dogs. Journal of Applied Physiology, 42, 403-407.

Wasserman, K. (1984a). Coupling of external to internal respiration. American Review of Respiratory Disease, 129 (Supplement), S21-S24.

Wasserman, K. (1984b). The anaerobic threshold measurement to evaluate exercise performance. American Review of Respiratory Disease, 129 (Suppl.), S35-S40.

Wasserman, K., & McIlroy, M. B. (1964). Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. American Journal of Cardiology, 14, 844-852.

Wasserman, K., Whipp, B. J., Koyal, S. N., & Beaver, W. L. (1973). Anaerobic threshold & respiratory gas exchange during exercise. Journal of Applied Physiology, 35, 236-243.

Wathen, R. L., Rostorfer, H. H., Robinson, S., Newton, J. L., & Bailie, M. D. (1962). Changes in blood gases & acid-base balance in exercising dogs. Journal of Applied Physiology, 17, 656-666.

Weibel, E. R. (1984). The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System. Cambridge, MA: Harvard University Press.

Winter, H. (1959). The pathology of canine dirofilariasis. American Journal of Veterinary Research, March, 366-371.

World Health Organization. (1961). WHO Technical Series Report on Chronic Cor Pulmonale, Definition & List of Suggested Causes. (No. 213).

Wylie, J. P. (1970). In R. E. Bradley (Ed.), Canine Heartworm Disease. A Discussion of the Current Knowledge. (pp. 109-114). Gainesville: Univ. of Fla.

Yin, F. P. C., Weisfeldt, M. L., & Milnor, W. R. (1981). Role of aortic input impedance in the decreased cardiovascular response to exercise with aging in dogs. Journal of Clinical Investigation, 68, 28-38.

Young, D. R., Mosher, R., Erve, P., & Spector, H. (1959). Energy metabolism & gas exchange during treadmill running in dogs. Journal of Applied Physiology, 14, 834-838.

Young, M. A., Hintz, T. H., & Vatner, S. F. (1985). Correlation between cardiac performance and plasma catecholamine levels in conscious dogs. American Journal of Physiology, 248, H82-H88.

APPENDIX A

Results of Diagnostic Tests

Table A-1

Means of Hemograms

PARAMETER	NORMAL RANGE	CONTROL VALUE	HEARTWORM VALUE
Erythrocytes (10^3/ul)	5.5-8.5	5.93 ±0.29	6.21 ±1.28
Hemoglobin (gm/dl)	12.0-18.0	12.75 ±0.51	13.48 ±2.86
Packed Cell Volume (%)	37.0-55.0	36.75 ±1.26	39.25 ±9.22
Mean Corpuscular Volume (fl)	60.0-77.0	64.75 ±1.89	65.50 ±1.00
Mean Corpuscular Haemoglobin (pg)	20.0-25.0	21.97 ±0.26	22.15 ±0.48
Mean Corpuscular Haemoglobin Concentration (gm/dl)	32.0-36.0	32.65 ±0.57	32.70 ±0.51
Leukocytes (10^3/ul)	6.0-17.0	16.78 ±4.20	15.88 ±5.68
Basophils (10^3/ul)	rare	none	0.20 (n=2)
Eosinophils (10^3/ul)	0.1-1.25	0.18 ±0.18	*1.05 ±0.55
Lymphocytes (10^3/ul)	1.0-4.8	5.43 ±0.40	**1.88 ±0.59
Monocytes (10^3/ul)	0.15-1.35	0.55 ±0.54	0.65 ±0.54
Neutrophils Band (10^3/ul)	0-3.0	0.08 ±0.10	0.05 ±0.10
Mature (10^3/ul)	3.0-11.5	10.55 ±4.25	12.15 ±5.62
Total Plasma Proteins (gm/dl)	6.0-7.8	6.73 ±0.17	**8.18 ±0.57

* = $p < .05$ ** = $p < .01$

The dog's normal range is that listed in Current Veterinary Therapy VIII (1983).

Table A-2

Means of Serum Chemical Profiles

PARAMETER	NORMAL RANGE	CONTROL VALUE	HEARTWORM VALUE
Serum Glucose (mg/dl)	60-100	80.25 ±9.74	82.75 ±11.35
Blood Urea Nitrogen (mg/dl)	10-20	10.75 ±2.36	13.75 ±1.71
Serum Glutamic Oxaloacetic Transaminase (SFu/ml)	13-93	21.00 ±3.92	21.25 ±9.84
Serum Glutamic Pyruvic Transaminase (SFu/ml)	15-70	14.50 ±2.52	65.75 ±49.97
Alkaline Phosphatase (IU/l)	10-82	43.50 ±5.45	68.00 ±39.34
Total Serum Protein (gm/dl)	6.0-7.8	5.73 ±0.25	**7.73 ±0.48
Albumin (gm/dl)	2.3-3.2	2.58 ±0.17	2.75 ±0.33
Creatinine (mg/dl)	1.0-2.0	0.63 ±0.13	0.60 ±0.14
Serum Electrolytes Calcium (mg/dl)	8.4-11.2	9.65 ±0.50	10.20 ±0.32
Phosphorus (mg/dl)	2.5-5.0	3.75 ±0.39	5.95 ±2.15
Sodium (mEq/l)	140-150	145.50 ±1.92	142.75 ±3.50
Potassium (mEq/l)	3.7-5.8	4.56 ±0.10	4.79 ±0.18
Chloride (mEq/l)	105-115	107.25 ±3.10	106.50 ±1.29

** = $p < .01$

The dog's normal range is that listed in Current Veterinary Therapy VIII (1983).

Table A-3

Means of Urinalysis

PARAMETER	NORMAL RANGE	CONTROL VALUE	HEARTWORM VALUE
Specific Gravity	1.015 to 1.045	1.017 ±0.01	**1.034 ±0.01
pH	5.0 to 7.0	7.75 ±1.19	7.50 ±0.58

** = $p < .05$

The dog's normal range is that listed in Current Veterinary Therapy VIII (1983).

APPENDIX B

Means and Standard Deviations of Variables

Table B-1

Heartworm Dogs' Means and Standard Deviations of Variables

Normal Exercise

Workload	n	Arterial Blood			
		pH	PCO_2 (mm Hg)	PO_2 (mm Hg)	HCO_3^- (mEq/L)
Rest	4	7.406 ±0.046	36.29 ±1.87	88.11 ±3.89	22.51 ±1.72
3 mph, 0%	4	7.454 ±0.038	32.30 ±2.34	86.85 ±8.56	22.15 ±1.90
4 mph, 0%	4	7.466 ±0.034	30.84 ±1.21	87.14 ±8.45	21.80 ±1.59
4 mph, 4%	4	7.456 ±0.021	31.94 ±1.47	86.61 ±8.68	22.01 ±1.21
4 mph, 8%	4	7.458 ±0.040	30.56 ±1.49	84.01 ±7.14	21.19 ±1.65
4 mph, 12%	4	7.460 ±0.036	31.15 ±1.41	83.73 ±8.24	21.65 ±1.38
4 mph, 16%	4	7.445 ±0.026	32.76 ±2.79	79.49 ±5.40	22.00 ±1.73
4 mph, 20%	4	7.446 ±0.023	32.34 ±2.33	80.34 ±13.02	21.73 ±1.74

Table B-2

Heartworm Dogs' Means and Standard Deviations of Variables

Normal Exercise

Workload	n	Venous Blood			
		pH	PCO_2 (mm Hg)	PO_2 (mm Hg)	HCO_3^- (mEq/L)
Rest	4	7.382 ±0.043	40.23 ±3.05	41.26 ±7.42	23.38 ±0.76
3 mph, 0%	4	7.392 ±0.029	34.26 ±3.92	31.89 ±4.35	22.00 ±1.89
4 mph, 0%	4	7.403 ±0.035	37.91 ±2.92	32.14 ±2.96	23.24 ±2.86
4 mph, 4%	4	7.404 ±0.032	39.90 ±3.01	31.46 ±2.34	23.94 ±1.73
4 mph, 8%	4	7.403 ±0.038	36.58 ±3.06	30.38 ±5.34	22.23 ±1.66
4 mph, 12%	4	7.395 ±0.030	37.51 ±4.85	32.50 ±1.44	22.36 ±2.50
4 mph, 16%	4	7.399 ±0.041	36.99 ±4.05	29.88 ±2.99	22.30 ±1.73
4 mph, 20%	4	7.392 ±0.032	39.03 ±2.43	30.83 ±0.98	23.21 ±2.35

Table B-3

Heartworm Dogs' Means and Standard Deviations of Variables

Normal Exercise

Workload	n	Arterial Blood Pressure		
		Systolic (mm Hg)	Diastolic (mm Hg)	Mean (mm Hg)
Rest	4	146.88 ±17.84	90.00 ±8.42	108.96 ±11.52
3 mph, 0%	4	188.13 ±20.14	111.25 ±18.09	136.88 ±18.23
4 mph, 0%	4	195.00 ±11.73	103.75 ±20.67	134.19 ±17.64
4 mph, 4%	4	187.50 ±17.44	100.00 ±16.71	129.16 ±15.08
4 mph, 8%	4	191.88 ±11.25	103.75 ±16.89	133.13 ±13.03
4 mph, 12%	4	193.13 ±25.03	101.25 ±12.99	131.86 ±14.96
4 mph, 16%	4	199.38 ±15.60	103.13 ±12.48	134.38 ±10.75
4 mph, 20%	4	201.25 ±10.10	106.25 ±13.62	137.70 ±9.97

Table B-4

Heartworm Dogs' Means and Standard Deviations of Variables

Normal Exercise

Workload	n	Heart Rate (bpm)	Hct (%)	Temp (°C)	Lactate (mM/L)
Rest	4	105.25 ±21.20	35.32 ±4.07	39.14 ±0.64	1.38 ±0.17
3 mph, 0%	4	183.38 ±21.80	38.78 ±7.57	39.20 ±0.61	1.40 ±0.23
4 mph, 0%	4	190.13 ±29.27	39.70 ±7.65	39.27 ±0.58	1.43 ±0.39
4 mph, 4%	4	202.00 ±38.41	39.39 ±6.40	39.29 ±0.56	1.36 ±0.20
4 mph, 8%	4	206.88 ±39.12	40.27 ±6.68	39.34 ±0.53	1.44 ±0.37
4 mph, 12%	4	218.38 ±40.75	40.70 ±6.45	39.55 ±0.45	1.49 ±0.25
4 mph, 16%	4	221.63 ±33.12	41.23 ±6.54	39.55 ±0.38	1.51 ±0.19
4 mph, 20%	4	235.25 ±37.62	41.77 ±7.27	39.64 ±0.31	1.57 ±0.24

Table B-5

Heartworm Dogs' Means and Standard Deviations of Variables

Normal Exercise

Workload	n	Glucose (mg/dl)	n	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)
Rest	2	87.57 ±8.98	4	142.94 ±3.54	4.78 ±0.18	106.69 ±1.39
3 mph, 0%	2	86.98 ±9.05	4	143.31 ±1.23	5.14 ±0.27	107.44 ±2.90
4 mph, 0%	2	88.95 ±4.30	4	142.94 ±0.90	5.10 ±0.27	105.94 ±1.43
4 mph, 4%	2	92.57 ±6.26	4	143.13 ±1.59	5.09 ±0.22	105.13 ±2.15
4 mph, 8%	2	96.39 ±12.27	4	142.81 ±0.66	5.14 ±0.22	105.44 ±1.91
4 mph, 12%	2	98.50 ±7.53	4	143.13 ±1.05	5.14 ±0.26	105.19 ±2.63
4 mph, 16%	2	96.28 ±12.27	4	142.75 ±1.55	5.16 ±0.22	106.63 ±1.70
4 mph, 20%	2	98.27 ±2.97	4	144.00 ±2.04	5.28 ±0.35	107.44 ±1.16

Table B-6

Control Dogs' Means and Standard Deviations of Variables

Normal Exercise

Workload	n	Arterial Blood			
		pH	PCO_2 (mm Hg)	PO_2 (mm Hg)	HCO_3^- (mEq/L)
Rest	4	7.404 ±0.036	36.76 ±2.85	101.44 ±6.78	22.40 ±2.30
3 mph, 0%	4	7.420 ±0.015	35.23 ±4.06	105.41 ±4.69	22.21 ±2.68
4 mph, 0%	4	7.435 ±0.025	34.35 ±2.74	106.74 ±4.65	22.43 ±1.97
4 mph, 4%	4	7.430 ±0.025	34.85 ±2.12	106.64 ±8.84	22.48 ±1.51
4 mph, 8%	4	7.431 ±0.027	34.60 ±2.39	104.65 ±6.2	22.36 ±1.50
4 mph, 12%	4	7.445 ±0.042	32.96 ±1.69	106.14 ±3.71	21.94 ±1.50
4 mph, 16%	4	7.457 ±0.042	32.43 ±2.92	109.01 ±6.11	22.06 ±1.15
4 mph, 20%	4	7.448 ±0.036	33.06 ±2.07	109.15 ±2.72	22.00 ±0.54

Table B-7

Control Dogs' Means and Standard Deviations of Variables

Normal Exercise

Workload	n	Venous Blood pH	PCO_2 (mm Hg)	PO_2 (mm Hg)	HCO_3^- (mEq/L)
Rest	4	7.377 ±0.029	40.63 ±4.11	46.39 ±9.52	23.19 ±1.38
3 mph, 0%	4	7.382 ±0.017	40.14 ±5.98	38.23 ±1.68	23.47 ±3.18
4 mph, 0%	4	7.393 ±0.029	37.60 ±5.48	36.41 ±2.21	22.26 ±2.72
4 mph, 4%	4	7.394 ±0.015	40.14 ±4.30	37.20 ±1.99	23.80 ±2.49
4 mph, 8%	4	7.389 ±0.018	39.58 ±4.23	34.93 ±2.26	23.21 ±2.60
4 mph, 12%	4	7.381 ±0.025	42.25 ±3.62	35.23 ±1.86	24.30 ±1.93
4 mph, 16%	4	7.380 ±0.020	40.36 ±5.51	34.60 ±1.73	23.25 ±3.09
4 mph, 20%	4	7.381 ±0.024	41.60 ±5.46	33.96 ±3.05	23.81 ±2.57

Table B-8

Control Dogs' Means and Standard Deviations of Variables

Normal Exercise

Workload	n	Arterial Blood Pressure		
		Systolic (mm Hg)	Diastolic (mm Hg)	Mean (mm Hg)
Rest	3	147.50 ±15.21	95.00 ±19.53	112.52 ±18.10
3 mph, 0%	3	175.00 ±18.03	105.83 ±20.21	128.90 ±19.18
4 mph, 0%	3	175.83 ±11.55	95.00 ±15.21	121.90 ±13.93
4 mph, 4%	3	183.30 ±22.68	96.67 ±17.02	126.65 ±19.70
4 mph, 8%	3	170.83 ±12.58	99.17 ±16.65	123.07 ±15.10
4 mph, 12%	3	172.50 ±16.40	96.67 ±16.65	121.97 ±16.34
4 mph, 16%	3	174.17 ±17.74	95.00 ±12.99	121.38 ±13.74
4 mph, 20%	3	176.67 ±18.09	95.80 ±12.33	122.80 ±14.26

Table B-9

Control Dogs' Means and Standard Deviations of Variables

Normal Exercise

Workload	n	Heart Rate (bpm)	Hct (%)	Temp (°C)	Lactate (mM/L)
Rest	4	112.00 ±15.00	38.00 ±2.17	39.04 ±0.38	1.06 ±0.12
3 mph, 0%	4	172.50 ±23.81	39.19 ±1.52	39.08 ±0.35	1.06 ±0.29
4 mph, 0%	4	182.50 ±35.63	39.22 ±1.69	39.15 ±0.33	0.99 ±0.27
4 mph, 4%	4	188.00 ±35.71	40.63 ±2.14	39.26 ±0.33	0.99 ±0.25
4 mph, 8%	4	198.88 ±39.41	41.06 ±1.79	39.34 ±0.32	0.94 ±0.18
4 mph, 12%	4	213.13 ±38.11	41.69 ±1.33	39.43 ±0.35	1.07 ±0.09
4 mph, 16%	4	219.50 ±41.50	42.03 ±1.00	39.56 ±0.33	1.31 ±0.21
4 mph, 20%	4	219.60 ±47.60	42.90 ±1.06	39.68 ±0.33	1.67 ±0.53

Table B-10

Control Dogs' Means and Standard Deviations of Variables

Normal Exercise

Workload	n	Glucose (mg/dl)	n	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)
Rest	2	93.08 ±7.46	4	145.44 ±2.13	4.56 ±0.10	107.06 ±2.90
3 mph, 0%	2	88.35 ±7.21	4	145.75 ±2.04	4.74 ±0.06	107.44 ±1.88
4 mph, 0%	2	89.87 ±10.67	4	147.40 ±3.22	4.86 ±0.08	108.60 ±1.48
4 mph, 4%	2	91.20 ±8.19	4	147.25 ±4.40	4.84 ±0.06	107.60 ±2.18
4 mph, 8%	2	94.13 ±6.81	4	147.80 ±2.49	4.93 ±0.07	108.69 ±1.01
4 mph, 12%	2	90.57 ±11.86	4	148.31 ±0.97	5.03 ±0.09	109.69 ±0.85
4 mph, 16%	2	96.81 ±8.29	4	148.50 ±0.91	5.06 ±0.14	110.44 ±0.85
4 mph, 20%	2	90.90 ±8.12	4	148.50 ±1.42	5.11 ±0.11	109.69 ±1.80

Table B-11

Heartworm Dogs' Means and Standard Deviations of Variables

Sham Infusion Exercise

Workload	n	Arterial Blood			
		pH	PCO_2 (mm Hg)	PO_2 (mm Hg)	HCO_3^- (mEq/L)
Pre-infusion	2	7.373 ±0.019	36.90 ±2.26	93.60 ±5.52	20.95 ±2.19
Rest	2	7.378 ±0.008	36.45 ±2.33	95.35 ±0.21	20.95 ±1.63
3 mph, 0%	2	7.419 ±0.024	33.90 ±3.25	82.15 ±1.20	21.55 ±3.18
4 mph, 0%	2	7.435 ±0.026	32.05 ±3.32	82.80 ±0.57	21.10 ±3.39
4 mph, 4%	2	7.418 ±0.035	32.00 ±0.57	75.80 ±6.36	20.20 ±1.27
4 mph, 8%	2	7.432 ±0.028	30.70 ±1.56	76.75 ±3.18	19.95 ±0.21
4 mph, 12%	2	7.433 ±0.056	31.90 ±0.28	75.55 ±4.03	20.90 ±2.40
4 mph, 16%	2	7.430 ±0.038	29.80 ±2.69	74.20 ±6.36	19.25 ±0.07
4 mph, 20%	2	7.428 ±0.054	30.60 ±3.25	71.35 ±9.26	19.70 ±0.28

Table B-12

Heartworm Dogs' Means and Standard Deviations of Variables

Sham Infusion Exercise

Workload	n	Venous Blood			
		pH	PCO_2 (mm Hg)	PO_2 (mm Hg)	HCO_3^- (mEq/L)
Pre-infusion	2	7.349 ±0.008	40.05 ±2.05	47.35 ±11.10	21.50 ±1.41
Rest	2	7.355 ±0.005	39.55 ±5.30	44.40 ±7.07	21.60 ±3.11
3mph, 0%	2	7.381 ±0.015	35.30 ±1.70	33.60 ±4.53	20.45 ±1.63
4 mph, 0%	2	7.379 ±0.023	32.05 ±2.05	36.15 ±3.46	18.55 ±2.19
4 mph, 4%	2	7.391 ±0.028	34.80 ±0.57	30.90 ±1.41	20.70 ±1.56
4 mph, 8%	2	7.376 ±0.019	38.55 ±6.29	31.60 ±1.98	22.15 ±4.60
4mph, 12%	2	7.381 ±0.035	36.90 ±2.12	31.00 ±0.42	21.45 ±2.90
4 mph, 16%	2	7.368 ±0.033	38.20 ±0.57	30.30 ±0.57	21.50 ±1.84
4 mph, 20%	2	7.375 ±0.030	38.65 ±5.16	29.35 ±2.62	22.15 ±4.45

Table B-13

Heartworm Dogs' Means and Standard Deviations of Variables

Sham Infusion Exercise

Workload	n	Arterial Blood Pressure		
		Systolic (mm Hg)	Diastolic (mm Hg)	Mean (mm Hg)
Pre-infusion	2	137.50 ±17.68	87.50 ±17.68	104.20 ±17.68
Rest	2	142.50 ±24.75	80.00 ±14.14	100.80 ±17.68
3 mph, 0%	2	187.50 ±17.68	92.50 ±10.61	124.15 ±12.94
4 mph, 0%	2	182.50 ±24.75	90.00 ±14.14	120.80 ±17.68
4 mph, 4%	2	182.50 ±31.82	80.00 ±14.14	114.15 ±20.01
4 mph, 8%	2	187.50 ±31.82	87.50 ±31.82	120.80 ±17.68
4 mph, 12%	2	192.50 ±31.82	85.00 ±14.14	120.85 ±20.01
4 mph, 16%	2	200.00 ±35.35	85.00 ±14.14	123.30 ±21.21
4 mph, 20%	2	182.50 ±3.54	90.00 ±21.21	120.85 ±15.34

Table B-14

Heartworm Dogs' Means and Standard Deviations of Variables

Sham Infusion Exercise

Workload	n	Heart Rate (bpm)	Hct (%)	Temp (°C)	Lactate (mM/L)
Pre-infusion	2	121.50 ±20.51	31.88 ±5.48	39.45 ±0.21	1.06 ±0.17
Rest	2	118.00 ±9.90	29.00 ±2.12	39.25 ±0.35	1.07 ±0.31
3 mph, 0%	2	188.00 ±0.00	30.45 ±3.11	39.20 ±0.28	1.10 ±0.34
4 mph, 0%	2	215.50 ±21.92	32.50 ±2.83	39.20 ±0.28	0.92 ±0.10
4 mph, 4%	2	232.00 ±25.46	32.88 ±2.30	39.20 ±0.28	0.94 ±0.25
4 mph, 8%	2	225.00 ±35.35	33.05 ±2.90	39.25 ±0.21	1.00 ±0.05
4 mph, 12%	2	237.00 ±32.53	33.20 ±3.46	39.30 ±0.28	1.06 ±0.08
4 mph, 16%	2	237.00 ±32.53	34.33 ±3.64	39.40 ±0.28	1.25 ±0.26
4 mph, 20%	2	235.00 ±21.21	34.50 ±3.54	39.40 ±0.42	1.10 ±0.19

Table B-15

Heartworm Dogs' Means and Standard Deviations of Variables

Sham Infusion Exercise

Workload	n	Glucose (mg/dl)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)
Pre-infusion	2	88.15 ±0.00	140.75 ±0.35	4.78 ±0.25	105.75 ±1.06
Rest	2	88.96 ±1.80	140.75 ±3.18	4.83 ±0.25	108.50 ±2.12
3 mph, 0%	2	88.38 ±2.29	140.50 ±2.12	5.25 ±0.35	110.00 ±3.54
4 mph, 0%	2	88.38 ±6.54	141.75 ±1.06	5.28 ±0.25	110.25 ±0.35
4 mph, 4%	2	95.78 ±11.76	139.00 ±2.12	5.28 ±0.25	106.50 ±2.12
4 mph, 8%	2	91.73 ±5.07	144.00 ±4.95	5.35 ±0.35	110.00 ±0.00
4 mph, 12%	2	86.53 ±1.31	143.25 ±3.18	5.30 ±0.28	108.50 ±2.12
4 mph, 16%	2	98.90 ±11.61	142.00 ±0.71	5.15 ±0.21	107.75 ±1.77
4 mph, 20%	2	91.16 ±5.23	141.75 ±0.35	5.25 ±0.07	110.00 ±2.83

Table B-16

Control Dogs' Means and Standard Deviations of Variables

Sham Infusion Exercise

Workload	n	Arterial Blood			
		pH	PCO_2 (mm Hg)	PO_2 (mm Hg)	HCO_3^- (mEq/L)
Pre-infusion	2	7.410 ±0.033	33.75 ±1.48	114.60 ±3.96	20.95 ±0.64
Rest	2	7.399 ±0.031	37.35 ±1.06	97.40 ±1.13	22.60 ±0.99
3 mph, 0%	2	7.410 ±0.040	35.85 ±2.62	101.30 ±1.13	22.25 ±0.64
4 mph, 0%	2	7.423 ±0.069	34.65 ±5.73	101.85 ±6.72	22.05 ±0.07
4 mph, 4%	2	7.415 ±0.045	35.05 ±3.18	106.05 ±4.81	21.85 ±0.21
4 mph, 8%	2	7.415 ±0.062	33.85 ±6.86	104.20 ±9.48	21.05 ±1.20
4 mph, 12%	2	7.454 ±0.410	30.50 ±2.55	120.50 ±7.07	20.90 ±0.28
4 mph, 16%	2	7.438 ±0.048	31.85 ±5.30	110.65 ±0.92	20.90 ±1.13
4 mph, 20%	2	7.430 ±0.040	32.55 ±4.60	107.55 ±0.49	20.95 ±0.92

Table B-16

Control Dogs' Means and Standard Deviations of Variables

Sham Infusion Exercise

Workload	n	Venous Blood			
		pH	PCO_2 (mm Hg)	PO_2 (mm Hg)	HCO_3^- (mEq/L)
Pre-infusion	2	7.413 ±0.064	35.30 ±8.34	47.25 ±3.46	21.80 ±1.98
Rest	2	7.377 ±0.023	31.10 ±3.39	45.90 ±9.62	18.00 ±2.97
3 mph, 0%	2	7.373 ±0.035	33.10 ±3.25	40.10 ±2.12	18.90 ±0.28
4 mph, 0%	2	7.364 ±0.038	38.55 ±2.90	35.10 ±5.09	21.55 ±0.35
4 mph, 4%	2	7.352 ±0.056	33.05 ±0.49	36.90 ±5.52	18.00 ±2.12
4 mph, 8%	2	7.359 ±0.030	40.00 ±3.68	35.75 ±6.72	21.95 ±0.35
4 mph, 12%	2	7.356 ±0.024	37.75 ±1.06	34.60 ±5.94	20.65 ±0.64
4 mph, 16%	2	7.362 ±0.030	37.95 ±6.01	34.30 ±4.95	20.95 ±1.77
4 mph, 20%	2	7.357 ±0.037	39.80 ±1.27	32.35 ±4.31	32.35 ±4.31

Table B-18

Control Dogs' Means and Standard Deviations of Variables

Sham Infusion Exercise

Workload	n	Arterial Blood Pressure		
		Systolic (mm Hg)	Diastolic (mm Hg)	Mean (mm Hg)
Pre-infusion	1	80.00	65.00	70.00
Rest	1	90.00	65.00	73.30
3 mph, 0%	1	90.00	40.00	56.70
4 mph, 0%	1	90.00	40.00	56.70
4 mph, 4%	1	90.00	40.00	56.70
4 mph, 8%	1	90.00	40.00	56.70
4 mph, 12%	1	90.00	30.00	50.00
4 mph, 16%	1	90.00	30.00	50.00
4 mph, 20%	1	80.00	35.00	50.00

Table B-19

Control Dogs' Means and Standard Deviations of Variables

Sham Infusion Exercise

Workload	n	Heart Rate (bpm)	Hct (%)	Temp (°C)	Lactate (mM/L)
Pre-infusion	2	104.50 ±14.85	33.05 ±3.96	39.05 ±0.07	1.43 ±0.28
Rest	2	121.50 ±20.51	32.55 ±2.90	38.90 ±0.14	1.23 ±0.35
3 mph, 0%	2	143.00 ±9.90	33.30 ±3.96	38.90 ±0.28	1.41 ±0.50
4 mph, 0%	2	150.00 ±0.00	34.05 ±3.46	38.95 ±0.35	1.24 ±0.19
4 mph, 4%	2	154.00 ±5.66	35.30 ±3.11	39.10 ±0.42	1.16 ±0.07
4 mph, 8%	2	150.00 ±0.00	35.40 ±4.24	39.15 ±0.49	1.48 ±0.05
4 mph, 12%	2	154.00 ±5.66	35.83 ±4.49	39.25 ±0.49	1.37 ±0.09
4 mph, 16%	2	150.00 ±0.00	36.33 ±5.20	39.35 ±0.49	1.60 ±0.05
4 mph, 20%	2	154.00 ±5.66	36.88 ±5.62	39.45 ±0.49	1.74 ±0.16

Table B-20

Control Dogs' Means and Standard Deviations

Sham Infusion Exercise

Workload	n	Glucose (mg/dl)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)
Pre-infusion	2	94.86 ±1.63	146.50 ±0.00	4.73 ±0.11	107.75 ±1.77
Rest	2	90.58 ±7.03	146.30 ±0.35	4.65 ±0.35	108.75 ±2.48
3 mph, 0%	2	93.93 ±7.85	145.50 ±2.83	4.95 ±0.00	109.00 ±2.83
4 mph, 0%	2	89.54 ±2.28	145.75 ±1.77	4.95 ±0.07	108.75 ±2.47
4 mph, 4%	2	92.31 ±2.29	145.00 ±2.12	5.00 ±0.14	106.75 ±1.77
4 mph, 8%	2	86.42 ±5.07	147.00 ±0.71	5.10 ±0.00	109.80 ±1.77
4 mph, 12%	2	87.94 ±3.90	146.75 ±1.06	5.25 ±0.07	107.75 ±1.06
4 mph, 16%	2	84.94 ±8.86	147.00 ±1.41	5.28 ±0.04	109.50 ±1.41
4 mph, 20%	2	89.65 ±3.10	145.25 ±2.47	5.18 ±0.18	106.50 ±0.00

Table B-21

Heartworm Dogs' Means and Standard Deviations of Variables

Beta-Blocked Exercise

Workload	n	Arterial Blood			
		pH	PCO_2 (mm Hg)	PO_2 (mm Hg)	HCO_3^- (mm Hg)
Pre-infusion	2	7.379 ±0.001	34.15 ±0.71	88.05 ±0.07	19.65 ±0.57
Rest	4	7.399 ±0.024	34.70 ±2.11	94.11 ±3.30	20.91 ±0.50
3 mph, 0%	4	7.439 ±0.011	30.33 ±1.68	94.00 ±8.92	20.03 ±1.31
4 mph, 0%	4	7.440 ±0.004	30.66 ±1.72	94.01 ±8.24	20.35 ±1.17
4 mph, 4%	4	7.447 ±0.029	30.04 ±3.14	95.96 ±6.88	20.25 ±1.77
4 mph, 8%	4	7.437 ±0.013	29.99 ±3.12	94.09 ±9.77	19.71 ±1.97
4 mph, 12%	4	7.439 ±0.019	29.80 ±1.67	93.41 ±9.09	19.66 ±1.36
4 mph, 16%	4	7.450 ±0.017	29.30 ±2.86	93.09 ±9.80	19.75 ±1.63
4 mph, 20%	4	7.441 ±0.019	29.91 ±3.39	90.41 ±11.77	19.66 ±1.63

Table B-22

Heartworm Dogs' Means and Standard Deviations of Variables

Beta-Blocked Exercise

Workload	n	Venous Blood			
		pH	PCO_2 (mm Hg)	PO_2 (mm Hg)	HCO_3^- (mEq/L)
Pre-infusion	2	7.363 ±0.004	40.80 ±3.82	47.93 ±6.97	22.48 ±1.87
Rest	4	7.365 ±0.020	39.06 ±2.31	39.18 ±3.65	21.80 ±1.11
3 mph, 0%	4	7.377 ±0.008	39.96 ±1.38	27.24 ±2.25	22.94 ±0.75
4 mph, 0%	4	7.363 ±0.012	39.66 ±3.56	27.51 ±3.04	22.01 ±1.51
4 mph, 4%	4	7.358 ±0.027	41.14 ±2.44	26.79 ±3.47	22.59 ±1.77
4 mph, 8%	4	7.353 ±0.030	41.59 ±3.34	26.18 ±3.33	22.09 ±1.53
4 mph, 12%	4	7.350 ±0.022	36.34 ±6.40	25.96 ±3.30	22.19 ±1.61
4 mph, 16%	4	7.361 ±0.017	40.16 ±2.07	27.60 ±2.44	22.04 ±0.32
4 mph, 20%	4	7.352 ±0.018	43.45 ±3.34	27.19 ±4.27	23.25 ±1.15

Table B-23

Heartworm Dogs' Means and Standard Deviations of Variables

Beta-Blocked Exercise

Workload	n	Arterial Blood Pressure		
		Systolic (mm Hg)	Diastolic (mm Hg)	Mean (mm Hg)
Pre-infusion	2	148.75 ±12.37	96.25 ±1.77	113.75 ±2.97
Rest	4	143.75 ±9.46	87.50 ±4.08	106.27 ±5.68
3 mph, 0%	4	174.38 ±6.25	120.63 ±4.33	120.63 ±1.41
4 mph, 0%	4	166.88 ±13.40	93.13 ±4.27	117.70 ±5.92
4 mph, 4%	4	161.25 ±12.33	89.38 ±2.39	113.33 ±3.80
4 mph, 8%	4	164.40 ±5.54	91.25 ±2.50	115.63 ±3.50
4 mph, 12%	4	167.50 ±11.73	90.00 ±5.40	115.83 ±7.17
4 mph, 16%	4	169.38 ±3.75	95.63 ±3.15	120.21 ±2.65
4 mph, 20%	4	174.40 ±11.61	96.88 ±2.39	122.69 ±4.87

Table B-24

Heartworm Dogs' Means and Standard Deviations

Beta-Blocked Exercise

Workload	n	Heart Rate (bpm)	Hct (%)	Temp (°C)	Lactate (mM/L)
Pre-infusion	2	117.50 ±7.07	34.16 ±1.96	39.63 ±0.53	1.42 ±0.21
Rest	4	94.25 ±11.67	33.77 ±3.23	39.38 ±0.38	1.39 ±0.52
3 mph, 0%	4	140.63 ±7.43	38.11 ±6.10	39.39 ±0.37	1.30 ±0.40
4 mph, 0%	4	149.88 ±7.92	39.14 ±6.58	39.44 ±0.31	1.33 ±0.48
4 mph, 4%	4	153.15 ±8.33	39.53 ±7.33	39.56 ±0.44	1.23 ±0.52
4 mph, 8%	4	153.63 ±12.30	39.57 ±6.13	39.73 ±0.49	1.24 ±0.44
4 mph, 12%	4	155.63 ±14.21	39.78 ±5.77	39.96 ±0.58	1.30 ±0.46
4 mph, 16%	4	156.25 ±14.86	39.43 ±5.94	40.14 ±0.64	1.17 ±0.44
4 mph, 20%	4	162.5 ±21.5	38.89 ±5.19	40.14 ±0.67	1.26 ±0.37

Table B-25

Heartworm Dogs' Means and Standard Deviations

Beta-Blocked Exercise

Workload	n	Glucose (mg/dl)	n	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)
Pre-infusion	2	84.28 ±6.95	2	142.88 ±0.88	4.54 ±0.30	105.13 ±0.53
Rest	2	99.68 ±14.64	4	141.69 ±1.61	4.87 ±0.43	107.44 ±1.64
3 mph, 0%	2	99.14 ±16.90	4	143.50 ±0.71	5.19 ±0.26	108.44 ±1.26
4 mph, 0%	2	98.77 ±14.26	4	141.94 ±1.46	5.56 ±0.39	106.69 ±1.23
4 mph, 4%	2	97.07 ±14.98	4	142.00 ±1.14	5.58 ±0.38	107.44 ±2.11
4 mph, 8%	2	96.08 ±11.05	4	142.38 ±1.36	5.63 ±0.40	108.30 ±0.92
4 mph, 12%	2	98.72 ±15.42	4	142.31 ±1.56	5.73 ±0.41	108.13 ±0.92
4 mph, 16%	2	98.16 ±13.62	4	141.38 ±2.38	5.73 ±0.39	107.60 ±1.30
4 mph, 20%	2	94.78 ±15.59	4	142.81 ±1.95	5.85 ±0.42	109.69 ±0.63

Table B-26

Control Dogs' Means and Standard Deviations of Variables

Beta-Blocked Exercise

Workload	n	Arterial Blood			
		pH	PCO_2 (mm Hg)	PO_2 (mm Hg)	HCO_3^- (mEq/L)
Pre-infusion	2	7.404 ±0.024	36.65 ±1.06	100.23 ±1.24	23.00 ±0.28
Rest	4	7.418 ±0.043	36.58 ±4.48	93.98 ±3.68	22.95 ±1.34
3 mph, 0%	4	7.437 ±0.026	34.55 ±3.85	110.50 ±7.10	22.59 ±1.36
4 mph, 0%	4	7.445 ±0.037	33.39 ±4.84	108.43 ±6.63	22.19 ±1.68
4 mph, 4%	4	7.451 ±0.051	32.85 ±6.23	106.48 ±1.06	21.75 ±1.91
4 mph, 8%	4	7.452 ±0.055	32.01 ±7.12	109.75 ±5.09	21.43 ±2.52
4 mph, 12%	4	7.432 ±0.032	33.55 ±3.84	107.41 ±15.37	21.60 ±1.29
4 mph, 16%	4	7.428 ±0.052	33.79 ±7.30	107.33 ±4.84	21.25 ±2.43
4 mph, 20%	4	7.450 ±0.023	32.59 ±4.43	109.30 ±2.57	21.91 ±2.02

Table B-27

Control Dogs' Means and Standard Deviations of Variables

Beta-Blocked Exercise

Workload	n	Venous Blood			
		pH	PCO_2 (mm Hg)	PO_2 (mm Hg)	HCO_3^- (mEq/L)
Pre-infusion	2	7.378 ±0.044	44.35 ±6.43	44.18 ±0.81	25.43 ±1.10
Rest	4	7.365 ±0.052	36.03 ±3.99	42.01 ±4.69	20.05 ±1.97
3 mph, 0%	4	7.358 ±0.029	35.68 ±7.87	32.71 ±5.87	19.61 ±4.68
4 mph, 0%	4	7.360 ±0.031	39.91 ±8.63	31.19 ±3.99	21.70 ±3.04
4 mph, 4%	4	7.351 ±0.039	40.51 ±5.80	31.10 ±7.12	21.66 ±2.24
4 mph, 8%	4	7.368 ±0.029	39.91 ±6.81	29.44 ±5.41	22.18 ±2.75
4 mph, 12%	4	7.350 ±0.030	43.25 ±5.96	28.34 ±5.44	23.03 ±2.16
4 mph, 16%	4	7.348 ±0.036	43.11 ±7.27	29.95 ±7.83	23.03 ±4.14
4 mph, 20%	4	7.353 ±0.024	41.95 ±3.91	29.01 ±5.62	22.65 ±2.04

Table B-28

Control Dogs' Means and Standard Deviations of Variables

Beta-Blocked Exercise

Workload	n	Arterial Blood Pressure		
		Systolic (mm Hg)	Diastolic (mm Hg)	Mean (mm Hg)
Pre-infusion	1	150.00	92.50	111.70
Rest	3	156.67 ±17.56	103.30 ±5.77	117.50 ±9.62
3 mph, 0%	3	178.30 ±25.54	100.00 ±5.00	120.28 ±14.70
4 mph, 0%	3	170.00 ±41.31	79.17 ±7.22	111.95 ±17.82
4 mph, 4%	3	165.83 ±23.76	87.50 ±4.33	115.55 ±13.33
4 mph, 8%	3	171.67 ±38.76	84.17 ±3.82	113.90 ±15.52
4 mph, 12%	3	180.83 ±53.75	88.30 ±7.64	116.12 ±17.90
4 mph, 16%	3	152.50 ±24.75	85.00 ±7.07	120.83 ±24.84
4 mph, 20%	3	165.00 ±17.68	87.50 ±3.54	120.56 ±13.80

Table B-29

Control Dogs' Means and Standard Deviations of Variables

Beta-Blocked Exercise

Workload	n	Heart Rate (bpm)	Hct (%)	Temp (°C)	Lactate (mM/L)
Pre-infusion	2	112.50 ±34.65	37.69 ±1.15	39.20 ±0.00	0.86 ±0.19
Rest	4	108.38 ±13.06	36.28 ±1.39	39.86 ±0.93	1.19 ±0.24
3 mph, 0%	4	135.63 ±9.62	37.59 ±1.78	39.93 ±0.90	1.20 ±0.47
4 mph, 0%	4	149.30 ±4.57	38.03 ±1.83	40.03 ±0.88	1.24 ±0.62
4 mph, 4%	4	152.38 ±7.36	38.56 ±2.32	40.06 ±0.92	1.07 ±0.31
4 mph, 8%	4	158.38 ±10.78	39.10 ±2.40	40.09 ±0.97	1.16 ±0.19
4 mph, 12%	4	156.00 ±4.02	39.63 ±3.26	40.13 ±1.02	1.44 ±0.49
4 mph, 16%	4	155.00 ±6.12	40.00 ±3.11	40.21 ±1.09	1.71 ±0.90
4 mph, 20%	4	156.88 ±8.00	40.38 ±3.02	40.14 ±0.84	1.15 ±0.22

Table B-30

Control Dogs' Means and Standard Deviations of Variables

Beta-Blocked Exercise

Workload	n	Glucose (mg/dl)	n	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)
Pre-infusion	2	90.87 ±14.96	2	145.25 ±0.35	4.66 ±0.19	109.50 ±0.00
Rest	2	107.24 ±9.36	4	144.31 ±2.31	4.97 ±0.14	107.56 ±2.40
3 mph, 0%	2	109.58 ±12.34	4	145.13 ±1.11	5.21 ±0.20	108.69 ±2.49
4 mph, 0%	2	106.60 ±12.16	4	144.38 ±1.45	5.25 ±0.15	108.30 ±4.76
4 mph, 4%	2	103.00 ±12.63	4	146.00 ±0.89	5.35 ±0.18	109.94 ±2.11
4 mph, 8%	2	99.07 ±16.87	4	145.94 ±1.30	5.37 ±0.12	110.31 ±2.70
4 mph, 12%	2	92.11 ±17.51	4	145.25 ±0.96	5.48 ±0.19	108.75 ±1.86
4 mph, 16%	2	90.95 ±14.98	4	145.88 ±1.16	5.52 ±0.22	110.00 ±1.78
4 mph, 20%	2	91.58 ±16.08	4	146.31 ±1.07	5.49 ±0.24	109.69 ±3.88

APPENDIX C

ANOVAS, Student Newman Keuls, and Paired t-Tests Tables for Normal Exercise

Table C-1

Normal Exercise

2 x 8 ANOVA For Arterial pH

Source	df	SS	F	p
Total	63	0.0747		
Subject (Group) Error	1	0.0036	0.49	.5100
Workload	6	0.0440	33.09	.0001
Group x Workload	7	0.0136	8.76	.0001
Error	42	0.0093		

Student-Newman-Keuls: Follow-up Test for Significant Workload Effect

Grouping	Mean	Workload
A	7.452	5
A	7.451	6
A	7.451	2
A	7.447	7
A	7.444	4
A	7.443	3
A	7.437	1
B	7.405	Rest

Means with the same letter are not significantly different.

Table C-2

Normal Exercise

2 x 8 ANOVA For Arterial PCO_2

Source	df	SS	F	p
Total	63	475.99		
Group	1	65.31	2.37	.1743
Subject (Group) Error	7	165.02	11.77	.0001
Workload	7	111.95	6.84	.0001
Group x Workload	7	35.54	2.17	.0565
Error	42	377.81		

Student-Newman-Keuls Test: Follow-up for Significant Workload Effect

Grouping	Mean	Workload
A	36.53	Rest
B	33.71	1
B	33.39	3
B	32.70	7
B	32.59	2
B	32.59	6
B	32.58	4
B	32.06	5

Means with same letter are not significantly different.

Table C-3

Normal Exercise

2 x 8 ANOVA For Arterial PO_2

Source	df	SS	F	p
Total	63	10389.83		
Group	1	7473.60	22.73	.0031
Subject (Group) Error	6	1973.60	28.85	.0001
Workload	7	63.01	0.79	.6000
Group x Workload	7	401.19	5.03	.0003
Error	42	478.80		

Table C-4

Normal Exercise

2 x 8 ANOVA For Arterial HCO_3^-

Source	df	SS	F	p
Total	63	145.58		
Group	1	2.01	0.10	.5100
Subject (Group) Error	6	117.83	40.78	.0001
Workload	7	3.20	0.95	.4796
Group x Workload	7	2.31	0.69	.6824
Error	42	20.22		

Table C-5

Normal Exercise

2 x 8 ANOVA For Venous pH

Source	df	SS	F	p
Total	63	0.0470		
Group	1	0.0020	0.31	.5998
Subject (Group) Error	6	0.0390	77.07	.0001
Workload	7	0.0030	4.29	.0012
Group x Workload	7	0.0002	0.26	.9676
Error	42	0.0440		

Table C-6

Normal Exercise

2 x 8 ANOVA For Venous PCO_2

Source	df	SS	F	p
Total	63	1128.48		
Group	1	98.88	1.06	.3428
Subject (Group) Error	6	559.50	12.63	.0001
Workload	7	90.41	1.75	.1235
Group x Workload	7	69.71	1.35	.2520
Error	42	309.98		

Table C-7

Normal Exercise

2 x 8 ANOVA For Venous PO_2

Source	df	F	F	p
Total	63	1910.84		
Group	1	335.12	9.84	.0201
Subject (Group) Error	6	204.28	2.59	.0316
Workload	7	798.90	8.69	.0001
Group x Workload	7	20.72	0.23	.9771
Error	42	551.81		

Student-Newman-Keuls Test: Follow-up for Significant Workload Effect

Grouping	Mean	Workload
A	43.83	Rest
B	35.06	1
B	34.33	3
B	34.28	2
B	33.86	5
B	32.65	4
B	32.39	7
B	32.24	6

Means with the same letter are not significantly different.

Table C-8

Normal Exercise

2 x 8 ANOVA For Venous HCO_3^-

Source	df	SS	F	p
Total	63	284.21		
Group	1	5.38	0.18	.6839
Subject (Group) Error	6	176.49	15.71	.0001
Workload	7	10.83	0.83	.5714
Group x Workload	7	12.89	0.98	.4558
Error	42	78.63		

Table C-9

Normal Exercise

2 x 8 ANOVA For Hematocrit

Source	df	SS	F	p
Total	63	1334.36		
Group	1	14.32	0.08	.7866
Subject (Group) Error	6	1072.39	129.93	.0001
Workload	7	178.39	18.57	.0001
Group x Workload	7	11.01	1.14	.3552
Error	42	57.78		

Student-Newman-Keuls Test: Follow-up for Significant Workload Effect

Grouping	Mean	Workload
A	42.34	7
B A	41.63	6
B A C	41.19	5
B D C	40.67	4
E D C	40.01	3
E D	39.46	2
E	38.98	1
F	36.66	Rest

Means with the same letter are not significantly different.

Table C-10

Normal Exercise

2 x 8 ANOVA For Heart Rate

Source	df	SS	F	p
Total	63	138940.75		
Group	1	805.14	0.10	.7670
Subject (Group) Error	6	50255.80	46.20	.0001
Workload	7	79553.38	62.68	.0001
Group x Workload	7	711.23	0.56	.7835
Error	42	7615.20		

Student-Newman-Keuls Test: Follow-up for Significant Workload Effect

Grouping	Mean	Workload
A	227.44	7
A	220.56	6
B A	215.75	5
B C	202.88	4
D C	195.00	3
D E	186.31	2
E	177.94	1
F	109.63	Rest

Means with the same letter are not significantly different.

Table C-11

Normal Exercise

2 x 8 ANOVA For Rectal Temperature

Source	df	SS	F	p
Total	63	11.65		
Group	1	0.03	0.02	.8969
Subject (Group) Error	6	8.67	94.16	.0001
Workload	7	2.25	20.99	.0001
Group x Workload	7	0.05	0.51	.8214
Error	42	0.64		

Student-Newman-Keuls Test: Follow-up for Significant Workload Effect

Grouping	Mean	Workload
A	39.66	7
B A	39.56	6
B C	39.43	5
D C	39.34	4
D C E	39.28	3
D E	39.21	2
E	39.14	1
E	39.09	Rest

Means with the same letter are not significantly different.

Table C-12

Normal Exercise

2 x 8 ANOVA For Sodium

Source	df	SS	F	p
Total	63	514.33		
Group	1	249.05	13.57	.0103
Subject (Group) Error	6	110.13	6.90	.0001
Workload	7	15.04	0.81	.5862
Group x Workload	7	28.32	1.52	.1870
Error	42	111.79		

Table C-13

Normal Exercise

2 x 8 ANOVA For Potassium

Source	df	SS	F	p
Total	63	3.97		
Group	1	0.75	3.55	.1085
Subject (Group) Error	6	1.27	19.05	.0001
Workload	7	1.37	17.69	.0001
Group x Workload	7	0.12	1.49	.1967
Error	42	0.47		

Student-Newman-Keuls Test: Follow-up for Significant Workload Effect

Grouping			Mean	Workload
	A		5.19	7
B	A		5.11	6
B	A	C	5.08	5
B		C	5.03	4
B		C	4.98	3
B		C	4.97	2
		C	4.94	1
D			4.67	Rest

Means with the same letter are not significantly different.

Table C-14

Normal Exercise

2 x 8 ANOVA For Chloride

Source	df	SS	F	p
Total	63	329.34		
Group	1	93.24	5.58	.0561
Subject (Group) Error	6	100.26	10.17	.0001
Workload	7	32.66	2.84	.0162
Group x Workload	7	34.14	2.97	.0128
Error	42	69.03		

Student-Newman-Keuls Test: Follow-up for Significant Workload Effect

Grouping		Mean	Workload
	A	108.56	7
	A	108.53	6
B	A	107.44	1
B	A	107.44	5
B	A	107.25	2
B	A	107.06	4
B	A	106.88	Rest
B		106.38	3

Means with the same letter are not significantly different.

Table C-15

Normal Exercise

2 x 8 ANOVA For Lactate

Source	df	SS	F	p
Total	63	6.83		
Group	1	1.56	5.01	.0665
Subject (Group) Error	6	1.87	8.09	.0001
Workload	7	1.28	4.73	.0006
Group x Workload	7	0.51	1.87	.0984
Error	42	1.62		

Student-Newman-Keuls Test: Follow-up for Significant Workload Effect

Grouping	Mean	Workload
A	1.62	7
B	1.41	6
B	1.28	5
B	1.23	1
B	1.22	Rest
B	1.21	2
B	1.19	4
B	1.17	3

Means with the same letter are not signifiacntly different.

Table C-16

Normal Exercise

2 x 8 ANOVA For Glucose

Source	df	SS	F	p
Total	31	821.80		
Group	1	4.79	0.03	.8738
Subject (Group) Error	2	259.92	6.35	.0109
Workload	7	60.25	0.37	.9852
Group x Workload	7	134.88	0.83	.5813
Error	14	325.96		

Table C-17

Normal Exercise

2 x 8 ANOVA For Systolic Blood Pressure

Source	df	SS	F	p
Total	55	25498.21		
Group	1	3472.11	2.10	.2071
Subject (Group) Error	5	8271.42	18.88	.0001
Workload	7	8733.18	14.24	.0001
Group x Workload	7	1097.01	1.79	.1208
Error	35	3066.60		

Student-Newman-Keuls Test: Follow-up for Significant Workload Effect

Grouping	Mean	Workload
A	190.71	7
A	188.57	6
A	186.79	2
A	185.71	3
A	184.29	5
A	182.86	4
A	182.50	1
B	147.14	Rest

Means with the same letter are not significantly different.

Table C-18

Normal Exercise

2 x 8 ANOVA For Diastolic Blood Pressure

Source	df	SS	F	p
Total	55	11733.48		
Group	1	8604.23	41.11	.0001
Subject (group) Error	5	942.77	3.22	.0097
Workload	7	268.22	0.92	.5063
Group x Workload	7	346.44	0.20	.6724
Error	35	1465.04		

Table C-19

Normal Exercise

2 x 8 ANOVA For Mean Arterial Blood Pressure

Source	df	SS	F	p
Total	55	12988.50		
Group	1	963.84	0.61	.4687
Subject (Group) Error	5	7846.42	41.65	.0001
Workload	7	2140.60	8.12	.0001
Group x Workload	7	447.73	1.70	.1417
Error	35	1318.58		

Student-Newman-Keuls Test: Follow-up for Significant Workload Effect

Grouping	Mean	Workload
A	133.46	1
A	131.31	7
A	128.92	2
A	128.81	4
A	128.81	6
A	128.10	3
A	127.62	5
B	110.49	Rest

Means with the same letter are not significantly different.

Table C-20

Normal Exercise

Paired t-Tests For Heartworm Dogs

Comparison: PARAMETER	Rest-->W 1	Δ%	Rest-->W 7	Δ%
Arterial				
pH	t_3=+8.28 p=.998 *	+0.65	t_3=+2.78 p=.966	+0.54
PCO_2	t_3=-6.75 p=.003 *	-11.26	t_3=-2.98 p=.029	-10.89
PO_2	t_3=-0.42 p=.352	-1.43	t_3=-1.63 p=.895	-8.82
HCO_3^-	t_3=-0.65 p=.352	-1.60	t_3=-1.63 p=.895	-3.47
Venous				
pH	t_3=+1.27 p=.852	+0.13	t_3=+1.18 p=.838	+0.12
PCO_2	t_3=-2.03 p=.068	-14.80	t_3=-0.77 p=.249	-2.98
PO_2	t_3=-2.61 p=.040	-22.72	t_3=-3.09 p=.027	-25.29
HCO_3^-	t_3=-1.39 p=.129	-5.90	t_3=-0.19 p=0.43	-0.73

alpha=.025

* = significant for $-t_{a/2}$=.0125 < p or p > $+t_{a/2}$=.9875

Table C-20 Continued

Comparison: PARAMETER	Rest-->W 1	Δ%	Rest-->W 7	Δ%
Heart Rate	t_3=+12.61 p=.9995	+74.23	t_3=7.49 p=.9975	+123.52
MABP	t_3=+3.13 p=.974	+25.62	t_3=7.59 p=.9976	+26.38
Hematocrit	t_3=+1.90 p=.9233	+9.80	t_3=+3.84 p=.9844	+18.26
Rectal Temperature	t_3=+2.61 p=.96	+0.15	t_3=+2.74 p=.964	+1.28
Sodium	t_3=+0.28 p=.60	+0.26	t_3=+1.31 p=.86	+0.71
Potassium	t_3=+2.86 p=.968	+7.42	t_3=+2.94 p=.97	+10.29
Chloride	t_3=+0.64 p=.715	+0.70	t_3=+1.53 p=.889	+0.70
Lactate	t_3=+0.16 p=.557	+1.26	t_3=+1.03 p=.81	+13.36
Glucose	t_1=+1.6 p=.823	+4.56	t_1=+0.96 p=.744	+10.58

alpha=.025

* = $-t_{\alpha/2}$=.0125 < p or p > $+t_{\alpha/2}$=.9875

Table C-21

Normal Exercise

Paired t-Tests For Control Dogs

Comparison: PARAMETER	Rest-->w 1	Δ%	Rest-->w 7	Δ%
Arterial				
pH	t_3=+1.38 p=.869	+0.21	t_3=+8.65 p=.998 *	+0.59
PCO_2	t_3=-1.07 p=.18	-4.18	t_3=-2.88 p=.032	-10.06
PO_2	t_3=+2.16 p=.940	+3.92	t_3=+3.47 p=.980	+7.60
HCO_3^-	t_3=-0.24 p=.414	-0.85	t_3=-0.43 p=.347	-1.79
Venous				
pH	t_3=+0.71 p=.74	+0.10	t_3=+0.49 p=.67	+0.06
PCO_2	t_3=-0.23 p=.42	+5.57	t_3=+0.50 p=.68	+6.68
PO_2	t_3=-1.70 p=.094	-17.6	t_3=-2.08 p=.065	-26.79
HCO_3^-	t_3=+0.26 p=.59	+1.16	t_3=+0.64 p=.72	+2.67

alpha=.025

* = $-t_{a/2}$=.0125 < p or p > $+t_{a/2}$=.9875

Table C-21 Continued

Comparison: PARAMETER	Rest-->w 1	Δ%	Rest-->w 7	Δ%
Heart Rate	t_3=+7.12 p=.9971 *	+54.02	t_3=+5.55 p=.9942 *	+96.09
MABP	t_2=+3.54 p=.981	+14.56	t_2=+4.64 p=.9906 *	+9.14
Hematocrit	t_3=+1.67 p=.922	+3.13	t_3=+3.77 p=.9837	+12.90
Temperature	t_3=+1.67 p=.90	+0.10	t_3=+4.59 p=.991 *	+1.64
Sodium	t_3=+0.30 p=.61	+0.22	t_3=+0.47 p=.66	+0.41
Potassium	t_3=+5.73 p=.995 *	+4.17	t_3=+5.32 p=.994	+12.12
Chloride	t_3=+0.29 p=.60	+0.75	t_3=+3.48 p=.98	+2.45
Lactate	t_3=-0.20 p=.49	-0.24	t_3=+2.43 p=.953	+58.02
Glucose	t_1=+0.63 p=.68	+4.22	t_1=-0.36 p=.39	-1.87

alpha=.025

* = significant for $-t_{\alpha/2}$=.0125 < p or p > $+t_{\alpha/2}$=.9875

Table C-22

Normal Exercise

2 x 8 ANOVA For Arterial Oxygen Saturation
(All %Oxygen Sat were calculated with Hb=15)

Source	df	SS	F	p
Total	63	158.41		
Group	1	63.50	5.60	.0558
Subject (Group) Error	6	68.04	38.00	.0001
Workload	7	5.16	2.47	.0324
Group x Workload	7	9.18	4.39	.0010
Error	42	12.54		

Student-Newman-Keuls Test: Follow-up of significant Workload Effect.

Grouping	Mean	Workload
A	96.95	2
B A	96.78	3
B A	96.76	1
B A	96.62	4
B A	96.60	5
B A	96.40	Rest
B A	96.20	6
B	96.04	7

Means with the same letter are not significantly different.

Table C-23

Normal Exercise

2 x 8 ANOVA For Venous Oxygen Saturation
(All %Oxygen Sat were calculated with Hb=15)

Source	df	SS	F	p
Total	63	4889.89		
Group	1	450.50	5.07	.0654
Subject (Group) Error	6	533.56	2.09	.0750
Workload	7	1981.56	6.65	.0001
Group x Workload	7	135.22	0.45	.8621
Error	42	1789.06		

Student-Newman-Keuls Test: Follow-up of significant Workload Effect.

Grouping	Mean	Workload
A	68.72	Rest
B	57.08	1
B	56.53	2
B	55.54	3
B	53.51	4
B	52.37	5
B	50.47	6
B	49.99	7

Means with the same letter are not significantly different.

APPENDIX D

ANOVAS and Student Newman Keuls Tables

for Sham Infusion Experiment

Table D-1

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Arterial pH

Source	df	SS	F	p
Total	63	.0656		
Group	1	.00002	0.02	.9052
Subject (Group) Error	2	.0374	113.78	.0001
Condition	1	.0001	0.01	.9291
Group X Condition	1	.0001	0.11	.7764
Subject(GroupXCondition)Error	2	.0022	6.60	.0045
Workload	7	.0172	14.93	.0001
Group x Workload	7	.0022	1.92	.1040
Condition x Workload	7	.0013	1.16	.3551
Group X Condition x Workload	7	.0005	0.46	.8573
Error	28	.0046		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	7.436	5
B A	7.434	6
B A	7.433	2
B A	7.428	7
B A	7.423	3
B A	7.423	4
B	7.416	1
C	7.382	Rest

Means with the same letter are not significantly different.

Table D-2

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Arterial PCO_2

Source	df	SS	F	p
Total	63	509.80		
Group	1	12.29	2.27	.2710
Subject (Group) Workload	2	177.96	27.07	.0001
Condition	1	0.03	0.01	.9450
Group x Condition	1	13.10	2.42	.2604
Subject(GroupxCondition)Error	2	10.84	1.65	.2104
Workload	7	145.60	6.33	.0002
Group x Workload	7	20.41	0.89	.5294
Condition x Workload	7	27.06	1.18	.3478
Group x Condition x Workload	7	10.47	0.45	.8583
Error	28	92.04		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	36.68	Rest
B	33.84	1
B	33.25	3
B	32.68	2
B	32.41	4
B	32.28	7
B	31.84	6
B	31.73	5

Means with the same letter are not significantly different.

Table D-3

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Arterial PO_2

Source	df	SS	F	p
Total	63	15213.05		
Group	1	11973.83	57.02	.0171
Subject (Group) Error	2	380.99	10.42	.0004
Condition	1	5.12	0.02	.8903
Group x Condition	1	2.03	0.01	.9306
Subject(GroupxCondition)Error	2	419.99	11.48	.0002
Workload	7	185.48	1.45	.2259
Group x Workload	7	1267.97	9.91	.0001
Condition x Workload	7	145.68	1.14	.3684
Group x Condition x Workload	7	319.92	2.50	.0397
Error	28	512.03		

Table D-4

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Arterial HCO_3^-

Source	df	SS	F	p
Total	63	84.40		
Group	1	3.54	5.06	.1500
Subject (Group) Error	2	27.88	16.22	.0001
Condition	1	0.02	0.03	.8690
Group x Condition	1	6.73	9.62	.0901
Subject(GroupxCondition)Error	2	1.40	0.81	.4536
Workload	7	5.35	0.89	.5278
Group x Workload	7	3.17	0.53	.8066
Condition x Workload	7	9.84	1.63	.1668
Group x Condition x Workload	7	2.39	0.40	.8959
Error	28	24.08		

Table D-5

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Venous pH

Source	df	SS	F	p
Total	63	0.0310		
Group	1	0.0001	0.24	.6709
Subject (Group) Error	2	0.0204	114.08	
Condition	1	0.0001	0.28	.6505
Group x Condition	1	0.0017	3.72	.1936
Subject(GroupxCondition)Error	2	0.0009	5.25	.0116
Workload	7	0.0014	2.21	.0645
Group x Workload	7	0.0020	3.21	.0126
Condition by Workload	7	0.0007	1.13	.3729
Group x Condition x Workload	7	0.0006	0.98	.4632
Error	28	0.0025		

Table D-6

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Venous PCO_2

Source	df	SS	F	p
Total	63	1016.03		
Group	1	14.39	0.63	.5091
Subject (Group) Error	2	290.46	24.67	.0001
Condition	1	64.90	2.86	.2327
Group x Condition	1	5.97	0.26	.6588
Subject(GroupxCondition)Error	2	45.34	3.85	.0333
Workload	7	153.94	3.74	.0056
Group x Workload	7	96.74	2.35	.0510
Condition x Workload	7	112.83	2.74	.0269
Group x Condition x Workload	7	66.61	1.62	.1719
Error	28	164.85		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping		Mean	Workload
	A	39.30	7
	A	38.99	5
	A	38.37	4
	A	38.37	Rest
	A	38.26	6
B	A	36.84	3
B	A	36.36	2
B		34.41	1

Means with the same letter are not significantly different.

Table D-7

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Venous PO_2

Source	df	SS	F	p
Total	63	1705.95		
Group	1	139.09	3.58	.1989
Subject (Group) Error	2	227.54	11.43	.0002
Condition	1	2.58	0.07	.8207
Group x Condition	1	4.23	0.11	.7727
Subject(GroupxCondition)Error	2	77.63	3.90	.0321
Workload	7	842.24	12.09	.0001
Group x Workload	7	76.90	1.10	.3882
Condition x Workload	7	21.48	0.31	.9442
Group x Condition x Workload	7	35.50	0.51	.8195
Error	28	278.76		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	44.09	Rest
B	36.73	1
B	35.79	2
B	34.44	3
B	34.11	4
B	33.01	5
B	32.64	6
B	31.95	7

Means with the same letter are not significantly different.

Table D-8

Sham Infusion Exercise

2 x 2 x 8 ANOVA for Venous HCO_3^-

Source	df	SS	F	p
Total	63	261.81		
Group	1	9.92	1.25	.3792
Subject (Group) Error	2	96.26	35.86	.0001
Condition	1	27.17	3.43	.2050
Group x Condition	1	0.05	0.01	.9435
Subject(GroupxCondition)Error	2	15.82	5.89	.0073
Workload	7	19.79	2.11	.0762
Group x Workload	7	16.80	1.79	.1294
Condition x Workload	7	25.72	2.74	.0269
Group x Condtion x Workload	7	12.70	1.35	.2641
Error	28	37.58		

Table D-9

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Hematocrit

Source	df	SS	F	p
Total	63	928.13		
Group	1	284.24	2.80	.2361
Subject (Group) Error	2	42.79	37.55	.0001
Condition	1	204.04	2.01	.2919
Group x Condition	1	48.96	0.48	.5591
Subject(GroupxCondition)Error	2	202.88	178.05	.0001
Workload	7	119.31	29.91	.0001
Group x Workload	7	4.12	1.03	.4305
Condition x Workload	7	4.83	1.21	.3295
Group x Condition x Workload	7	1.01	0.25	.9673
Error	28	15.95		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping		Mean	Workload
	A	37.31	7
B	A	37.01	6
B	C	36.36	5
	C	35.90	4
D	C	35.55	3
D		34.85	2
	E	33.95	1
	F	33.12	Rest

Means with the same letter are not significantly different.

Table D-10

Sham Infusion Experiment

2 x 2 x 8 ANOVA For Heart Rate

Source	df	SS	F	p
Total	63	112245.93		
Group	1	40577.07	65.43	.0149
Subject (Group) Error	2	4504.29	14.41	.0001
Condition	1	988.32	1.59	.3341
Group x Condition	1	2922.75	4.71	.1621
Subject(GroupxCondition)Error	2	1240.35	3.97	.0304
Workload	7	48169.09	44.02	.0001
Group x Workload	7	6883.34	6.29	.0002
Condition x Workload	7	1403.34	1.28	.2948
Group x Condition x Workload	7	1179.90	1.08	.4031
Error	28	4377.48		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping		Mean	Workload
	A	204.56	7
	A	202.94	6
	A	202.44	5
B	A	192.81	4
B	A	191.38	3
B		183.19	2
	C	169.75	1
	D	116.38	Rest

Means with the same letter are not significantly different.

Table D-11

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Mean Arterial Blood Pressure

Source	df	SS	F	p
Total	47	30411.51		
Group	1	14982.51	14.80	.1619
Subject (Group) Error	2	1556.82	123.46	.0001
Condition	1	6349.84	6.27	.2419
Group x Condition	1	6387.98	6.31	.2412
Subject(GroupxCondition)Error	2	1012.50	80.30	.0001
Workload	7	328.45	3.72	.0174
Group x Workload	7	807.02	9.14	.0003
Condition x Workload	7	337.08	3.82	.0158
Group x Condition x Workload	7	295.09	3.34	.0260
Error	14	176.54		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	110.98	7
A	109.71	6
A	109.58	1
A	109.31	4
A	107.09	2
A	106.53	5
A	104.30	3
B	97.48	Rest

Means with the same letter are not significantly different.

Table D-12

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Systolic Blood Pressure

Source	df	SS	F	p
Total	47	71691.67		
Group	1	37406.51	28.48	.1179
Subject (Group) Error	1	4163.28	36.46	.0001
Condition	1	9063.26	6.90	.2316
Group x Condition	1	12489.84	9.51	.1996
Subject(GroupxCondition)Error	1	1313.28	11.50	.0044
Workload	7	3747.66	4.69	.0068
Group x Workload	7	1799.74	2.25	.0929
Condition x Workload	7	810.16	1.01	.4626
Group x Condition x Workload	7	216.41	0.27	.9554
Error	14	1598.44		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	171.67	6
A	168.75	7
A	167.08	4
A	165.42	5
A	164.58	2
A	162.92	3
A	160.42	1
B	132.50	Rest

Means with the same letter are not significantly different.

Table D-13

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Diastolic Blood Pressure

Source	df	SS	F	p
Total	47	18561.98		
Group	1	7570.38	8.63	.2088
Subject (Group) Error	1	726.76	50.97	.0001
Condition	1	5167.63	5.89	.2487
Group x Condition	1	4101.63	4.68	.2757
Subject(GroupxCondition)Error	1	876.75	61.49	.0001
Workload	7	335.87	3.37	.0254
Group x Workload	7	507.23	5.08	.0048
Condition x Workload	7	429.62	4.30	.0097
Group x Condition x Workload	7	375.98	3.77	.0166
Error	14	199.61		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	84.17	1
B A	82.08	7
B A	80.42	4
B A	80.00	Rest
B A	78.75	6
B A	78.33	2
B A	77.08	5
B	75.00	3

Means with the same letter are not significantly different.

Table D-14

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Rectal Temperature

Source	df	SS	F	p
Total	63	10.23		
Group	1	0.87	10.39	.0843
Subject (Group) Error	2	5.72	450.27	.0001
Condition	1	2.08	24.97	.0378
Group x Condition	1	0.09	1.12	.4002
Subject(GroupxCondition)Error	2	0.17	13.13	.0001
Workload	7	0.92	20.59	.0001
Group x Workload	7	0.14	3.08	.0156
Condition x Workload	7	0.05	1.09	.3973
Group x Condition x Workload	7	0.02	0.34	.9267
Error	28	0.18		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping			Mean	Workload
	A		39.61	7
B	A		39.53	6
B	C		39.44	5
D	C		39.39	4
D	C	E	39.35	3
D		E	39.29	2
		E	39.26	1
		E	39.26	Rest

Means with the same letter are not significantly different.

Table D-15

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Sodium

Source	df	SS	F	p
Total	63	599.87		
Group	1	333.06	45.83	.0211
Subject (Group) Error	2	77.25	12.66	.0001
Condition	1	10.16	1.40	.3586
Group x Condition	1	0.25	0.03	.8700
Subject(GroupxCondition)Error	2	14.54	2.38	.1109
Workload	7	31.29	1.46	.2202
Group x Workload	7	18.52	0.87	.5443
Condition x Workload	7	18.39	0.86	.5487
Group x Condition x Workload	7	10.95	0.51	.8172
Error	28	85.46		

Table D-16

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Potassium

Source	df	SS	F	p
Total	63	4.38		
Group	1	0.88	266.27	.0037
Subject (Group) Error	2	0.91	39.21	.0001
Condition	1	0.16	46.97	.0206
Group x Condition	1	0.08	22.91	.0410
Subject(GroupxConditon)Error	2	0.01	0.29	.7537
Workload	7	1.72	21.29	.0001
Group x Workload	7	0.20	2.47	.0416
Condition x Workload	7	0.05	0.57	.7728
Group x Condition x Workload	7	0.06	0.77	.6149
Error	28	0.32		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping		Mean	Workload
	A	5.23	7
	A	5.21	5
B	A	5.16	4
B	A	5.15	6
B	A	5.08	3
B	A	5.07	2
B		5.03	1
	C	4.68	Rest

Means with the same letter are not significantly different.

Table D-17

Sham Infusion Experiment

2 x 2 x 8 ANOVA For Chloride

Source	df	SS	F	p
Total	63	288.23		
Group	1	29.57	8.01	.1054
Subject (Group) Error	2	5.68	0.91	.4156
Condition	1	12.25	3.32	.2100
Group x Condition	1	69.10	18.73	.0495
Subject(GroupxCondition)Error	2	7.38	1.18	.3227
Workload	7	26.05	1.19	.3413
Group x Workload	7	15.56	0.71	.6641
Condition x Workload	7	28.06	1.28	.2958
Group x Condition x Workload	7	6.90	0.31	.9411
Error	28	87.70		

Table D-18

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Lactate

Source	df	SS	F	p
Total	63	3.89		
Group	1	0.04	0.17	.1701
Subject (Group) Error	2	0.02	0.37	.6971
Condition	1	0.03	0.13	.7574
Group x Condition	1	1.44	6.87	.1199
Subject(GroupxCondition)Error	2	0.42	6.41	.0051
Workload	7	0.59	2.58	.0346
Group x Workload	7	0.20	0.87	.5452
Condition x Workload	7	0.14	0.63	.7276
Group x Condition x Workload	7	0.09	0.40	.8912
Error	28	0.92		

Table D-19

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Glucose

Source	df	SS	F	p
Total	63	1852.08		
Group	1	26.52	1.17	.3921
Subject (Group) Error	2	465.15	8.79	.0011
Condition	1	5.23	0.23	.6798
Group X Condition	1	4.35	0.19	.7055
Subject(GroupxCondition)Error	2	45.76	0.87	.4319
Workload	7	87.73	0.47	.8451
Group x Workload	7	172.17	0.93	.4990
Condition x Workload	7	94.09	0.51	.8240
Group x Condition x Workload	7	210.31	1.14	.3695
Error	28	740.46		

Table D-20

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Arterial Oxygen Saturation
(All %Oxygen Sat were calculated with Hb=15 gm.)

Source	df	SS	F	p
Total	63	230.00		
Group	1	160.97	61.56	.0159
Subject (Group) Error	2	7.16	6.57	.0046
Condition	1	0.60	0.23	.6790
Group x Condition	1	0.24	0.09	.7915
Subject(GroupxCondition)Error	2	5.23	4.80	.0162
Workload	7	11.30	2.96	.0187
Group x Workload	7	24.04	6.30	.0002
Condition x Workload	7	2.11	0.55	.7879
Group x Condition x Workload	7	3.10	0.81	.5847
Error	28	15.26		

Student-Newman-Keuls Test: Follow-up on significant Workload Effect.

Grouping		Mean	Workload
	A	96.51	2
	A	96.35	Rest
	A	96.26	1
B	A	96.11	5
B	A	96.05	3
B	A	96.03	4
B	A	95.69	6
B		95.08	7

Means with the same letter are not sifnificantly different.

Table-D-22

Sham Infusion Exercise

2 x 2 x 8 ANOVA For Venous Oxygen Saturation
(All %Oxygen Sat were calculated with Hb=15 gm)

Source	df	SS	F	p
Total	63	4712.54		
Group	1	627.19	5.18	.1506
Subject (Group) Error	2	149.07	2.65	.0886
Condition	1	2.38	0.02	.9013
Group x Condition	1	0.41	0.00	.9587
Subject(GroupxCondition)Error	2	242.15	4.30	.0236
Workload	7	2439.11	12.37	.0001
Group x Workload	7	224.97	1.14	.3668
Condition x Workload	7	109.70	0.56	.7843
Group x Condition x Workload	7	128.82	0.65	.7086
Error	28	788.74		

Student-Newman-Keuls Test: Follow-up of significant Workload Effect.

Grouping	Mean	Workload
A	39.30	7
A	38.99	5
A	38.37	4
A	38.37	Rest
A	38.26	6
B A	36.84	3
B A	36.16	2
B	34.41	1

Means with the same letter are not significantly different.

APPENDIX E

MANOVAS, ANOVAS, Wilks'-Lambda Criterion Tests,

Student-Newman-Keuls, and Paired *t*-Tests Tables

for Beta Blocked vs Normal Exercise

Table E-1

Beta Blocked vs Normal Exercise

2 x 2 x 8 MANOVA For Arterial Blood Gas and pH

Source	df	F	p
Overall Group	4, 3	11.90	.0348
Overall Condition	4, 3	3.56	.1627
Overall Group x Condition	4, 3	1.79	.3295
Overall Workload	28, 293^	2.75^	.0001
Overall Group x Workload	28, 293^	2.15^	.0010
Overall Condition x Workload	28, 293^	0.84^	.6983
Overall Group x Condition x Workload	28, 293^	0.95^	.5476

^ = approximate value

Table E-2

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA for Arterial pH

Source	df	SS	F	p
Total	127	0.1358		
Group	1	0.0012	0.13	.7328
Subject (Group) Error	6	0.0582	22.33	.0001
Condition	1	0.0004	0.29	.6123
Group x Conditon	1	0.0025	1.92	.2151
Subject(GroupxCondition)Error	6	0.0077	2.95	.0015
Workload	7	0.0209	6.88	.0001
Group x Workload	7	0.0024	0.77	.6103
Condition x Workload	7	0.0018	0.60	.7527
Group x Condition x Workload	7	0.0042	1.39	.2210
Error	84	0.0365		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	7.447	2
A	7.446	3
A	7.446	7
A	7.445	6
A	7.445	4
A	7.444	5
A	7.437	1
B	7.407	Rest

Means with the same letter are not significantly different.

Table E-3

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Arterial PCO_2

Source	df	SS	F	p
Total	127	1669.22		
Group	1	207.44	2.81	.1446
Subject (Group) Error	6	442.63	16.40	.0001
Condition	1	41.80	0.82	.4001
Group x Condition	1	8.85	0.17	.6915
Subject(GroupxCondition)Error	6	305.94	11.33	.0001
Workload	7	228.04	7.24	.0001
Group x Workload	7	18.80	0.60	.7566
Condition x Workload	7	7.76	0.25	.9721
Group x Condition x Workload	7	30.07	0.95	.4694
Error	84	377.89		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	36.08	Rest
B	33.08	1
B	32.42	3
B	32.31	2
B	32.07	6
B	31.98	7
B	31.87	5
B	31.79	4

Means with the same letter are not significantly different.

Table E-4

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Arterial PO_2

Source	df	SS	F	p
Total	127	17745.65		
Group	1	9589.39	17.68	.0057
Subject (Group) Error	6	3254.05	26.91	.0001
Condition	1	737.28	7.86	.0310
Group x Condition	1	592.11	6.31	.0458
Subject(GroupxCondition)Error	6	562.98	4.66	.0004
Workload	7	271.89	1.93	.0752
Group x Workload	7	737.29	5.23	.0001
Condition x Workload	7	169.26	1.20	.3120
Group x Condition x Workload	7	138.51	0.98	.4500
Error	84	1692.88		

Table E-5

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Arterial HCO_3^-

Source	df	SS	F	p
Total	127	391.84		
Group	1	41.29	3.54	.1088
Subject (Group) Error	6	69.90	17.52	.0001
Condition	1	35.81	1.44	.2749
Group x Condition	1	19.53	0.79	.4091
Subject(GroupxCondtion)Error	6	148.85	37.30	.0001
Workload	7	13.78	2.96	.0080
Group x Workload	7	1.33	0.28	.9583
Condition x Workload	7	2.62	0.56	.7839
Group x Condition x Workload	7	2.87	0.62	.7415
Error	84	55.86		

Student-Newman Keuls Test: Follow-up of significant Workload Effect.

Grouping		Mean	Workload
	A	22.19	Rest
B	A	21.74	1
B	A	21.69	2
B	A	21.62	3
B		21.33	7
B		21.27	6
B		21.21	5
B		21.17	4

Means with the same letter are not significantly different.

Table E-6

Beta Blocked vs Normal Exercise

2 x 2 x 8 MANOVA for Venous Blood Gas and pH

Source	df	F	p
Overall Group	4, 3	1.02	.5147
Overall Condition	4, 3	17.69	.0200
Overall Group x Condition	4, 3	0.13	.9603
Overall Workload	28, 293^	6.20^	.0001
Overall Group x Workload	28, 293^	0.99^	.4849
Overall Condition x Workload	28, 293^	1.56^	.0395
Overall Group x Condition x Workload	28, 293^	0.78^	.7798

^ = approximate value

Table E-7

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Venous pH

Source	df	SS	F	p
Total	127	0.1240		
Group	1	0.016	0.19	.6814
Subject (Group) Error	6	0.0528	39.39	.0001
Condition	1	0.0337	19.58	.0044
Group x Condiition	1	0.0005	0.30	.6043
Subject(GroupxCondition)Error	6	0.0103	7.70	.0001
Workload	7	0.0019	1.21	.3087
Group x Workload	7	0.0008	0.54	.8054
Condition x Workload	7	0.0028	1.81	.0959
Group x Condition x Workload	7	0.0008	0.52	.8188
Error	84	0.0188		

Table E-8

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Venous PCO_2

Source	df	SS	F	p
Total	127	2807.73		
Group	1	44.53	0.25	.6336
Subject (Group) Error	6	1060.31	20.88	.0001
Conditon	1	36.23	0.56	.4813
Group x Condition	1	54.60	0.85	.3924
Subject(GroupxCondition)Error	6	385.91	7.60	.0001
Workload	7	162.25	2.74	.0131
Group x Workload	7	143.74	2.43	.0259
Condition x Workload	7	104.17	1.76	.1067
Group x Condition x Workload	7	104.92	1.77	.1039
Error	84	711.06		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	41.51	7
B A	40.42	3
B A	40.16	6
B A	39.84	5
B A	39.41	4
B A	38.98	Rest
B A	38.77	2
B	37.51	1

Means with the same letter are not significantly different.

Table E-9

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Venous PO_2

Source	df	SS	F	p
Total	127	4956.82		
Group	1	491.80	4.45	.0793
Subject (Group) Error	6	662.55	11.99	.0001
Condition	1	719.63	10.75	.0168
Group x Condition	1	13.78	0.21	.6659
Subject(GroupxCondition)Error	6	401.54	7.26	.0001
Workload	7	1818.60	28.20	.0001
Group x Workload	7	37.07	0.57	.7745
Condition x Workload	7	34.32	0.53	.8079
Group x Condition x Workload	7	3.73	0.06	.9997
Error	84	773.80		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	42.21	Rest
B	32.52	1
B	31.81	2
B	31.64	3
B	30.51	6
B	30.51	5
B	30.25	7
B	30.23	4

Means with the same letter are not significantly different.

Table E-10

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Venous HCO_3^-

Source	df	SS	F	p
Total	127	642.60		
Group	1	0.02	0.00	.9809
Subject (Group) Error	6	157.61	10.60	.0001
Condition	1	36.71	1.46	.2720
Group x Condition	1	11.61	0.46	.5218
Subject(GroupxCondition)Error	6	150.58	10.12	.0001
Workload	7	22.64	1.30	.2582
Group x Workload	7	22.60	1.30	.2592
Condition x Workload	7	14.32	0.83	.5690
Group x Condition x Workload	7	18.27	1.05	.4011
Error	84	208.22		

Table E-11

Beta Blocked vs Normal Exercise

2 x 2 x 8 MANOVA For Hematocrit, Heart Rate, Mean Arterial Blood Pressure, and Rectal Temperature

Source	df	F	p
Overall Group	4, 2	0.29	.8681
Overall Condition	4, 2	3.89	.2146
Overall Group x Condition	4, 2	1.84	.3818
Overall Workload	28, 243^	15.98^	.0001
Overall Group x Workload	28, 243^	1.93^	.0046
Overall Condition x Workload	28, 243^	3.62^	.0001
Overall Group x Condition x Workload	28, 243^	1.14^	.2890

^ = approximate value

Table E-12

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Hematocrit

Source	df	SS	F	p
Total	111	2390.91		
Group	1	18.61	0.06	.8221
Subject (Group) Error	5	1656.90	229.26	.0001
Condition	1	19.76	0.45	.5327
Group x Condition	1	2.15	0.05	.8339
Subject(GroupxCondition)Error	5	220.24	30.47	.0001
Workload	7	321.05	31.73	.0001
Group x Workload	7	25.03	2.47	.0250
Condition x Workload	7	8.94	0.88	.5238
Group x Condition x Workload	7	4.35	0.43	.8800
Error	70	101.18		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	41.20	7
A	40.87	6
B A	40.64	5
B A C	40.12	4
B C	39.66	3
D C	39.09	2
D	38.43	1
E	35.52	Rest

Means with the same letter are not significantly different.

Table E-13

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Heart Rate

Source	df	SS	F	p
Total	111	218529.10		
Group	1	158.13	0.03	.8732
Subject (Group) Error	5	28025.90	48.64	.0001
Condition	1	67810.41	19.52	.0069
Group x Condition	1	0.24	0.00	.9937
Subject(GroupxCondition)Error	5	17372.06	30.15	.0001
Workload	7	81255.53	100.72	.0001
Group x Workload	7	828.84	1.03	.4200
Condition x Workload	7	10953.73	13.58	.0001
Group x Condition x Workload	7	214.66	0.27	.9650
Error	70	8067.24		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	198.21	7
B A	191.21	6
B A	188.93	5
B C	182.39	4
D C	176.07	3
D	169.89	2
E	160.32	1
F	105.57	Rest

Means with the same letter are not significantly different.

Table E-14

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Mean Arterial Blood Pressure

Source	df	SS	F	p
Total	111	21887.58		
Group	1	420.48	0.26	.6302
Subject (Group) Error	5	8005.95	54.46	.0001
Condition	1	2715.20	92.35	.0001
Group x Condition	1	547.55	0.69	.4447
Subject(GroupxCondition)Error	5	3981.10	27.08	.0001
Workload	7	2157.62	10.48	.0001
Group x Workload	7	683.34	3.32	.0041
Condition x Workload	7	592.90	2.88	.0106
Group x Condition x Workload	7	55.79	0.27	.9632
Error	70	2058.16		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	126.97	1
A	126.54	7
A	124.64	6
A	122.08	2
A	121.85	4
A	121.79	5
A	121.18	3
B	110.78	Rest

Means with the same letter are not significantly different.

Table E-15

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Rectal Temperature

Source	df	SS	F	p
Total	111	54.47		
Group	1	0.65	0.19	.6819
Subject (Group) Error	5	17.20	167.93	.0001
Condition	1	14.62	6.01	.0578
Group x Condition	1	3.40	1.40	.2905
Subject(GroupxCondition)Error	5	12.16	118.74	.0001
Workload	7	5.04	35.17	.0001
Group x Workload	7	0.23	1.62	.1447
Condition x Workload	7	0.05	0.32	.9413
Group x Condition x Workload	7	0.66	4.61	.0003
Error	70	1.43		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	39.98	7
A	39.89	6
B	39.74	5
C	39.62	4
D C	39.53	3
D E	39.45	2
E	39.38	1
E	39.33	Rest

Means with the same letter are not significantly different.

Table E-16

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Systolic Blood Pressure

Source	df	SS	F	p
Total	109	54605.74		
Group	1	545.84	0.17	.6972
Subject (Group) Error	5	16049.32	32.19	.0001
Condition	1	3585.32	2.11	.2060
Group x Condition	1	3370.13	1.98	.2180
Subject(GroupxCondition)Error	5	8494.17	17.04	.0001
Workload	7	10828.40	15.51	.0001
Group x Workload	7	786.47	1.13	.3568
Condition x Workload	7	1461.18	2.09	.0559
Group x Condition x Workload	7	504.69	0.72	.6528
Error	70	6779.90		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	181.73	7
A	179.29	1
A	178.75	5
A	177.50	2
A	177.12	6
A	175.18	4
A	174.46	3
B	148.21	Rest

Means with the same letter are not significantly different.

Table E-17

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Diastolic Blood Pressure

Source	df	SS	F	p
Total	109	16561.65		
Group	1	375.89	0.45	.5312
Subject (Group) Error	5	4157.74	28.10	.0001
Condition	1	2157.89	2.55	.1710
Group x Condition	1	40.06	0.05	.8363
Subject(GroupxCondition)Error	5	4226.27	28.57	.0001
Workload	7	974.20	4.70	.0002
Group x Workload	7	1131.88	5.46	.0001
Condition x Workload	7	657.81	3.18	.0058
Group x Condition x Workload	7	216.55	1.05	.4084
Error	68	2012.57		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	102.68	1
B	98.08	7
B	96.15	6
B	95.00	4
B	94.29	5
B	93.57	2
B	93.57	3
B	93.21	Rest

Means with the same letter are not significantly different.

Table E-18

Beta Blocked vs Normal Exercise

2 x 2 x 8 MANOVA For Electrolytes

Source	df	F	p
Overall Group	3, 4	9.61	.0267
Overall Condition	3, 4	132.78	.0002
Overall Group x Condition	3, 4	0.23	.8720
Overall Workload	21, 236^	8.51^	.0001
Overall Group x Workload	21, 236^	1.74^	.0256
Overall Condition x Workload	21, 236^	1.77^	.0221
Overall Group x Condition x Workload	21, 236^	1.47^	.0894

^ = approximate value

Table E-19

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Sodium

Source	df	SS	F	p
Total	127	858.05		
Group	1	402.57	26.83	.0021
Subject (Group) Error	6	90.02	7.75	.0001
Condition	1	51.89	4.21	.0859
Group x Condition	1	5.08	0.41	.5445
Subject(GroupxCondition)Error	6	73.91	6.37	.0001
Workload	7	18.45	1.36	.2322
Group x Workload	7	29.68	2.19	.0430
Condition x Workload	7	13.33	0.98	.4485
Group x Condition x Workload	7	10.62	0.78	.6022
Error	84	162.52		

Table E-20

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Potassium

Source	df	SS	F	p
Total	127	18.72		
Group	1	1.31	1.83	.2251
Subject (Group) Error	6	4.28	41.79	.0001
Condition	1	5.83	77.20	.0001
Group x Condition	1	0.01	0.09	.7762
Subject(GroupxCondition)Error	1	0.45	4.42	.0006
Workload	7	4.59	38.39	.0001
Group x Workload	7	0.14	1.15	.3428
Condition x Workload	7	0.33	2.80	.0115
Group x Condition x Workload	7	0.34	2.84	.0105
Error	84	1.43		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	5.43	7
B A	5.37	6
B A	5.34	5
B C	5.27	4
C	5.22	3
C	5.19	2
D	5.07	1
E	4.79	Rest

Means with the same letter are not significantly different.

Table E-21

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Chloride

Source	df	SS	F	p
Total	127	697.8		
Group	1	104.22	3.91	.0955
Subject (Group) Error	6	160.12	15.82	.0001
Condition	1	39.94	1.93	.2141
Group x Condition	1	11.88	0.57	.4773
Subject(GroupxCondition)Error	6	124.18	12.27	.0001
Workload	7	48.09	4.07	.0007
Group x Workload	7	37.11	3.14	.0053
Condition x Workload	7	17.89	1.52	.1732
Group x Conditon x Workload	7	12.77	1.08	.3822
Error	84	141.67		

Student-Newman-Keuls Test: Follow-up for significant Workload Effetc.

Grouping	Mean	Workload
A	109.13	7
B A	108.65	6
B A C	108.19	4
B A C	108.00	1
B A C	107.94	5
B C	107.53	3
B C	107.38	2
C	107.19	Rest

Means with the same letter are not significantly different.

Table E-22

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Lactate

Source	df	SS	F	p
Total	127	18.86		
Group	1	0.81	1.22	.3112
Subject (Group) Error	6	3.99	11.39	.0001
Condition	1	0.01	0.01	.9215
Group x Condition	1	0.75	0.86	.3905
Subject(GroupxCondition)Error	6	5.25	14.97	.0001
Workload	7	1.02	2.50	.0221
Group x Workload	7	0.74	1.80	.0970
Condition x Workload	7	0.76	1.85	.0887
Group x Condition x Workload	7	0.57	1.40	.2179
Error	84	4.91		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	1.42	6
A	1.41	7
A	1.33	5
A	1.25	Rest
A	1.25	2
A	1.24	1
A	1.20	4
A	1.16	3

Means with the same letter are not significantly different.

Table E-23

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Glucose

Source	df	SS	F	p
Total	63	8746.34		
Group	1	31.32	0.04	.8635
Subject (Group) Error	2	1648.80	27.44	.0001
Condition	1	4592.98	19.12	.0485
Group x Condition	1	75.53	0.31	.6314
Subject(GroupxCondition)Error	2	480.32	7.99	.0018
Workload	7	259.24	1.23	.3185
Group x Workload	7	317.82	1.51	.2041
Condition x Workload	7	395.60	1.88	.1108
Group x Condition x Workload	7	103.62	0.49	.8317
Error	28	841.11		

Table E-24

Beta Blocked Exercise

Paired t-Tests For Heartworm Dogs

Comparison: PARAMETER	Rest-->w 1	Δ%	Rest-->w 7	Δ%
Arterial				
pH	t_3=+6.14 p=.996 *	+0.54	t_3=+2.91 p=.969	+0.57
PCO_2	t_3=-3.90 p=.015	-12.60	t_3=-3.17 p=.025	-13.80
PO_2	t_3=-0.04 p=.49	-0.11	t_3=-0.86 p=.23	-3.90
HCO_3^-	t_3=-1.47 p=.12	-4.20	t_3=-1.93 p=.07	-5.70
Venous				
pH	t_3=+1.71 p=.91	+0.16	t_3=-1.19 p=.16	-0.18
PCO_2	t_3=+1.73 p=.91	+2.30	t_3=+7.55 p=.9976 *	+11.20
PO_2	t_3=-5.23 p=.007 *	-30.55	t_3=-2.06 p=.066	-30.60
HCO_3^-	t_3=+3.50 p=.98	+5.20	t_3=+3.87 p=.985	+6.7

alpha=.025

* = significant for $-t_{a/2}$=.0125 < p or p > $+t_{a/2}$=.9875

Table E-24 Continued

Comparison: PARAMETER	Rest-->w 1	Δ%	Rest-->w 7	Δ%
Heart Rate	t_3=+21.72 p=.9999 *	+49.10	t_3=+8.95 p=.9986	+72.30
MABP	t_3=+5.18 p=.993 *	+13.50	t_3=+5.36 p=.994 *	+15.40
SBP	t_3=+14.35 p=.9996 *	+21.30	t_3=+6.82 p=.997 *	+21.30
DBP	t_3=+1.89 p=.922	+7.20	t_3=+3.38 p=.984	+10.70
Hematocrit	t_3=+2.01 p=.93	+12.90	t_3=+3.62 p=.982	+15.20
Temperature	t_3=+0.33 p=.62	+0.03	t_3=+4.59 p=.9903 *	+2.46
Sodium	t_3=+2.45 p=.954	+1.30	t_3=+0.97 p=.80	+0.78
Potassium	t_3=+3.87 p=.988 *	+6.57	t_3=+4.33 p=.989 *	+20.12
Chloride	t_3=+1.35 p=.87	+0.93	t_3=+2.48 p=.955	+2.14
Lactate	t_3=+0.76 p=.75	-6.50	t_3=+0.93 p=.79	-9.40
Glucose	t_3=-0.42 p=.35	-0.19	t_3=-1.44 p=.12	-3.40

alpha=.025

* = significant for $-t_{\alpha/2}$=.0125 < p or p > $+t_{\alpha/2}$=.9875

Table E-25

Beta Blocked Exercise

Paired t-Tests For Control Dogs

Comparison: PARAMETER	Rest-->w 1	Δ%	Rest-->w 7	Δ%
Arterial				
pH	t_3=+1.86 p=.92	+0.26	t_3=+1.73 p=.91	+0.43
PCO_2	t_3=-1.68 p=.096	-5.50	t_3=-2.77 p=.035	-10.90
PO_2	t_3=+5.76 p=.995 *	+17.60	t_3=+8.19 p=.998 *	+16.30
HCO_3^-	t_3=-0.40 p=.36	-1.57	t_3=-1.11 p=.18	-4.60
Venous				
pH	t_3=-0.33 p=.38	-0.10	t_3=-0.57 p=.30	-0.16
PCO_2	t_3=-0.13 p=.45	-0.97	t_3=+6.31 p=.996 *	+16.40
PO_2	t_3=-3.69 p=.017	-22.14	t_3=-20.81 p=.0001 *	-30.90
HCO_3^-	t_3=-0.18 p=.43	-2.20	t_3=+1.90 p=.923	+12.96

alpha=.025

* = significant for $-t_{a/2}$=.0125 < p or p > $+t_{a/2}$=.9875

Table E-25 Continued

Comparison: PARAMETER	Rest-->w 1	Δ%	Rest-->w 7	Δ%
Heart Rate	t_3=+5.67 p=.995 *	+23.70	t_3=+5.35 p=.994 *	+43.20
MABP	t_2=+0.54 p=.68	+2.40	t_2=+0.62 p=.71	+2.60
SBP	t_2=+2.08 p=.91	+13.80	t_2=+1.70 p=.88	+5.30
DBP	t_2=-0.76 p=.25	-3.20	t_2=-8.00 p=.008 *	-15.30
Hematocrit	t_3=+2.75 p=.965	+4.10	t_3=+2.97 p=.97	+13.60
Temperature	t_3=+1.67 p=.90	+0.22	t_3=+2.02 p=.93	+0.97
Sodium	t_3=+0.81 p=.76	+0.55	t_3=+1.48 p=.81	+1.39
Potassium	t_3=+8.66 p=.998 *	+4.83	t_3=+5.09 p=.993 *	+10.50
Chloride	t_3=+2.90 p=.969	+1.02	t_3=+1.58 p=.894	+1.95
Lactate	t_3=+0.06 p=.52	+0.84	t_3=+1.74 p=.91	-3.36
Glucose	t_3=+0.48 p=.67	+6.90	t_3=-2.30 p=.053	-11.50

alpha=.025

* = significance for $-t_{a/2}$=.0125 < p or p > $+t_{a/2}$=.9875

Table E-26

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Arterial Oxygen Saturation (Hb=15)

Source	df	SS	F	p
Total	127	231.90		
Group	1	69.69	5.90	.0512
Subject (Group) Error	2	70.84	28.52	.0001
Condition	1	7.34	2.64	.1551
Group x Condition	1	8.53	3.07	.1301
Subject(GroupxCondition)Error	6	16.66	6.71	.0001
Workload	7	9.65	3.33	.0035
Group x Workload	7	8.51	2.94	.0085
Condition x Workload	7	1.82	0.63	.7312
Group x Condition x Workload	7	4.09	1.41	.2119
Error	84	34.77		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping		Mean	Workload
	A	97.12	2
	A	97.09	3
B	A	97.03	1
B	A	96.92	4
B	A	96.78	5
B	A	96.51	6
B	A	96.48	7
B		96.40	Rest

Means with the same letter are not significantly different.

Table E-27

Beta Blocked vs Normal Exercise

2 x 2 x 8 ANOVA For Venous Oxygen Saturation (Hb=15)

Source	df	SS	F	p
Total	127	17361.28		
Group	1	880.95	2.74	.1486
Subject (Group) Error	6	1925.70	10.65	.0001
Condition	1	4717.70	38.31	.0008
Group x Condition	1	0.11	0.00	.9768
Subject(GroupxCondition)Error	6	738.83	4.08	.0012
Workload	7	6020.89	28.53	.0001
Group x Workload	7	146.79	0.70	.6756
Condition x Workload	7	363.17	1.72	.1150
Group x Condition x Workload	7	34.70	0.16	.9915
Error	84	2532.29		

Student-Newman-Keuls Test: Follow-up for significant Workload Effect.

Grouping	Mean	Workload
A	66.54	Rest
B	50.89	1
B C	49.83	2
B D C	48.42	3
D C	45.79	4
D C	45.10	5
D C	44.98	6
D	44.09	7

Means with the same letter are not significantly different.

VITA

Patricia Louise Hopkins Price was born on December 26, 1949 in New Orleans, Louisiana. She matriculated from Academy of the Sacred Heart in June, 1967. She attended the University of Texas at Austin from 1967 to 1969, before transferring to H. Sophie Newcomb College in New Orleans. She received a Bachelors of Arts degree in Economics from Newcomb College in 1971.

Patricia worked for oil and chemical companies and was a tourguide in New Orleans. She resumed studies part-time in the Education Department of Loyola University in New Orleans the spring semester of 1976, and transferred to Tulane University in New Orleans in August, 1976. While attending Tulane, Patricia was an assistant teacher in social studies and science at Academy of the Sacred Heart, and was coaching swimming in New Orleans. She earned a Bachelor of Arts degree in Physical Education from Tulane University in 1978.

Patricia continued to coach swimming and to work as a tourguide before commencing graduate studies at Louisiana State University in Baton Rouge in the spring of 1979, where she was a graduate assistant in the Department of Health, Physical Education and Recreation. She completed her Master of Science in Exercise Physiology in August, 1980. She continued graduate studies in the School of Health, Physical Education, Recreation and Dance, pursuing a doctoral degree. In May, 1986, Patricia completed the Ph.D. degree in exercise physiology with a minor in veterinary physiology.

DOCTORAL EXAMINATION AND DISSERTATION REPORT

Candidate: Patricia Louise Hopkins Price

Major Field: HPERD (Exercise Physiology)

Title of Dissertation: The Effects of Heartworm Infection and Beta Blockade on Submaximal, Graded Exercise in Dogs

Approved:

Major Professor and Chairman

Dean of the Graduate School

EXAMINING COMMITTEE:

Date of Examination:

April 30, 1986